IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

EXHIBITS TO THE DECLARATION OF KAREN JACOBS LOUDEN
IN SUPPORT OF WYETH'S OPENING MARKMAN BRIEF

VOLUME 3 OF 3

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EXHIBIT 15

IN 992374

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 24, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: ***09/950,965***
FILING DATE: ***September 12, 2001***
PATENT NUMBER: ***6,403,120***
ISSUE DATE: ***June 11, 2002***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WOODSON
Certifying Officer

11000 U.S. PTO
09/950965
09/12/01

Class	Subclass	ISSUE CLASSIFICATION
424	461	

PATENT NUMBER
6403120
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U.S. UTILITY Patent Application

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PATENT DATE
JUN 11 2002

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/950965	D	424	461	1615	SPEAR

APPLICANTS
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John Clark
John Lamer
Steven White
09/884,412

TITLE
Extended release formulation

PTO-2040
12/99

ISSUING CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)
424	461	424	457 458 459
INTERNATIONAL CLASSIFICATION			
A61K 9/52		514	781 962
A61K 9/24			
A61K 9/62			

☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER

☐ The term of this patent subsequent to _____ (date) has been disclaimed.

☐ The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____

☐ The terminal ____ months of this patent have been disclaimed.

DRAWINGS Sheets Drwg.	Figs. Drwg.	Print Fig.	CLAIMS ALLOWED Total Claims	Print Claim for O.G.
0	0	0	14	1

NOTICE OF ALLOWANCE MAILED
03-19-02

(Assistant Examiner) (Date)

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

James M. Spear 3-19-02
(Primary Examiner) (Date)

ISSUE FEE mr

Amount Due	Date Paid
1580	4/12/02

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Form PTO-436A
(Rev. 6/99)

FILED WITH: ☐ DISK (CRF) ☐ FICHE ☐ CD-ROM
(Attached in pocket on right inside flap)

Issue Fee

Issue Fee

Issue Fee

WYETH 002-000345

(FACE)

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 2886

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/950,965	09/12/2001 RULE	424	1615	AHP-95011 C1

APPLICANTS

Deborah M. Sherman, Plattsburgh, NY;
John C. Clark, Peru, NY;
John U. Lamer, St. Albans, VT;
Steven A. White, Champlain, NY;

** CONTINUING DATA **********

THIS APPLICATION IS A CON OF 09/884,412 06/19/2001
WHICH IS A DIV OF 09/488,629 01/20/2000 PAT 6,274,171
WHICH IS A CIP OF 08/964,328 11/05/1997 ABN
WHICH IS A CIP OF 08/821,137 03/20/1997 ABN
WHICH CLAIMS BENEFIT OF 60/014,006 03/25/1996

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 10/11/2001

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☐ yes ☑ no	NY		13	2
35 USC 119 (a-d) conditions met	☐ yes ☑ no ☐ Met after Allowance				
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS

25291

TITLE

Extended release formulation OF VENLAFAXINE HYDROCHLORIDE

348-02

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
710		

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

11/5/01

09/17/2001 NMOHAMM1 00000015 011425 09950965
01 FC:101 710.00 CH

PTO-1556
(5/87)

*U.S. GPO: 1999-459-082/19144

09-14-01

Docket No: AHP-95011 C1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	Deborah M. Sherman, John C. Clark, John U. Lamer, Stephen A. White	
Serial No.:	Not Yet Known	Group Art No.:
Filed:	herewith	Examiner:
For:	Extended Release Formulation	
Confirmation No.:		
Customer Number:	25291	

Commissioner for Patents
Box PATENT APPLICATION
Washington, DC 20231

APPLICATION FOR TRANSMITTAL UNDER 37 CFR 1.53 (B)

Transmitted herewith for filing is the patent application of the following Inventor(s):
Deborah M. Sherman, John C. Clark, John U. Lamer, Stephen A. White;
For: Extended Release Formulation.

1. This new application is for a:
   - ☐ Divisional
   - ☒ Continuation
   - ☐ Continuation-in-part (CIP)

2. Benefit of Prior U.S. Application(s) (35 USC 120)
   This new application being transmitted claims the benefit of prior U.S. application(s) Serial No. 09/884,412, filed on June 19, 2001.

3. Papers enclosed which are required for filing date under 35 CFR 1.53(b):
   - ☒ Pages of specification – 23 pages
   - ☐ Sequence Listing – pages on
     - ☐ CD-ROM or CD-R (2 copies); or
     - ☐ Paper
   - ☒ Pages of claims – 4 pages
   - ☒ Page(s) of abstract – 1 pages
   - Sheets of drawing – pages
     - ☐ Formal
     - ☐ Informal

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EM474059865US addressed to the Commissioner for Patents, Box PATENT APPLICATION, Washington, DC 20231.

September 12, 2001
Date

Mary Ellen Fiala
Mary Ellen Fiala

4. Additional papers enclosed
- ☒ Information Disclosure Statement
- ☒ Form PTO-1449
- ☐ Citations
- ☐ Declaration of Biological Deposit
- ☐ Computer Readable Form of Sequence Listing
- ☐ Declaration Under 37 CFR 1.821(f)
- ☒ Other: Preliminary Amendment

5. Declaration
- ☒ Copy from a prior application (37 CFR 1.63 (d)) is enclosed
- ☐ New declaration enclosed and executed by all inventor(s)
- ☐ New declaration not enclosed or not executed by all inventor(s)

6. Assignment
An assignment of the invention to:
American Home Products Corporation

- ☒ was made in the prior application and recorded in PTO on March 7, 2001, Reel 011368, Frame 0195; and June 5, 2001, Reel 011866, Frame 0884.
- ☐ is attached under separate Recordation Form Cover Sheet.
- ☐ will follow.

7. Incorporation By Reference
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Section 5 of this transmittal, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

8. Amendments
- ☐ Cancel in this application original claims of the prior application before calculating the filing fee. (At least one original independent claim is retained for filing purposes.)
- ☒ A preliminary amendment is enclosed. (Claims added by this amendment have been properly numbered consecutively beginning with the number next following with the highest numbered original claim in the prior application.)

9. General Authorization:
During the pendency of this application treat any reply requiring a petition for extension of time for its timely submission as containing a request therefor for the appropriate length of time. The Commissioner is hereby authorized to charge all required extension of time fees during the entire pendency of this application to Deposit Account No. 01-1425

10. Filing Fee Calculation

CLAIMS AS AMENDED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA x RATE		(4) BASIC FEE
				$710.00
TOTAL CLAIMS	13	0	x $ 18.00	0.00
INDEPENDENT CLAIMS	3		x $ 80.00	0.00
MULTIPLE DEPENDENCY FEE			$ 270.00	
			Total Filing Fee:	$710.00

11. Fee payment being made at this time: $710.00

12. Method of Payment of Fees:
Charge Deposit Account No. 01-1425 in the amount of $710.00
A duplicate of this transmittal is attached.

13. Instructions as to Overpayment:
Credit any overpayment to Deposit Account No. 01-1425.

14. Authorization to Charge Additional Fees
☒ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Deposit Account No. 01-1425:
☒ 37 CFR 1.16(a), (f), or (g) filing fees
☒ 37 CFR 1.16(b), (c), and (d) presentation of extra claims
☒ 37 CFR 1.16(e) surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application.
☒ 37 CFR 1.17 application processing fees

15. Relate Back (35 USC 120)
☒ Amend the Specification by inserting before the first line the sentence:
--This is a continuation of copending application(s) serial number 09/884,412 filed on June 19, 2001 the entire disclosure of which is hereby incorporated by reference.--

16. Further Inventorship Statement Where Benefit of Prior Application(s) Claimed
(a) ☐ This application discloses and claims only subject matter disclosed in the prior application whose particulars are set out above and the inventor(s) in this application is (are)
☐ the same
☐ less than those named in the prior application and it is requested that the following inventor(s) identified for the prior application be deleted in accordance with the signed statement attached deleting inventor(s) named in the prior application (see 37 CFR 1.63(d)(2) and 1.33(b)):

(b) ☐ This application discloses and claims additional disclosure by amendment and a new declaration is being filed. With respect to the prior application the inventor(s) in this application is (are)
☐ the same
☐ the following additional inventors have been added:

17. Maintenance of Copendency of Prior Application
(a) ☐ Extension of Time in Prior Application
☐ A petition, fee and response extends the term in the pending prior application until .
☐ A copy of the petition filed in the prior application is attached.

(b) ☐ Conditional petition for Extension of Time in Prior Application.
☐ A conditional petition for extension of time is being filed in the pending prior application.
☐ A copy of the conditional petition filed in the prior application is attached.

18. **REQUEST AND CERTIFICATION UNDER 35 U.S.C 122(b)(2)(B)(i).**
☐ **A request not to publish this application and certification under 35 U.S.C. 122(b)(2)(B)(i) is attached.**

19. SEND CORRESPONDENCE TO:
Customer Number: 25291

Bar Code: 25291 PATENT TRADEMARK OFFICE

DIRECT ALL TELEPHONE CALLS TO:
Name: Rebecca R. Barrett
Tel. No. 610-902-2646

20. ☒ Return Receipt Postcard is attached.

Rebecca R. Barrett

Rebecca R. Barrett

Reg. No. 35,152

American Home Products Corporation
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. 610-902-2646

WYETH 002-000351

20 January 2000
SRE/rlk/apr
AHP-95011-P2
PATENT

EXTENDED RELEASE FORMULATION

This application continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, which is a continuation-in-part of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Background of the Invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to

form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day , in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was

greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of

total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70 % to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w) , with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis.

Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55°C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which

could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride–microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

Example No. 1.

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

Example No. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example No. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example No. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

Table 1
Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules

are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

Table 2
Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3.
Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Example No. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in

combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

Example No. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Kentucky 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Maryland 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

Time/hr	% Dissoluded 16.5% / 5%	% Dissolved 16.5% / 7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

Example No. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25% / 5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

3. An extended release formulation according to Claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to Claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to Claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose,

7. An extended release formulation according to Claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP

8. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose

9. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to Claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55

8	55-80
12	65-90
24	>80

12. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

13. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. A composition according to claim 2 wherein the film coating comprises 6-8% by weight of total weight.

15. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcelluiose (0.437% of total weight).

16. A composition according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

17. A film coating composition according to Claim 2 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. A film coating composition according to Claim 2 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropylmethylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

20. An extended release formulation of venlafaxine hydrochloride according to Claim 2 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

21. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

ABSTRACT OF THE DISCLOSURE

EXTENDED RELEASE FORMULATION

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

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DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is the invention entitled EXTENDED RELEASE FORMULATION, the specification of which

(check one) _____ is attached hereto.

X was filed on January 20, 2000 as
Application Serial No 09/488,629
and was last amended on February 16, 2001 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56 (a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

			Priority Claimed	
			Yes	No
NONE				
(Number)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

60/014,006	March 25, 1996
(Provisional Appln. No.)	(Filing Date)
(Provisional Appln. No.)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

AHP-95011 P2
PATENT

08/821,137 (Application Serial No.)	3/20/97 (Filing Date)	Abandoned (Status - Patented, pending, abandoned)
08/964,328 (Application Serial No.)	11/5/97 (Filing Date)	Abandoned (Status - Patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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WYETH 002-000377

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,403,120 B1**
(45) **Date of Patent: Jun. 11, 2002**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/950,965**

(22) Filed: **Sep. 12, 2001**

Related U.S. Application Data

(63) Continuation of application No. 09/884,412, filed on Jun. 19, 2001, which is a division of application No. 09/488,629, filed on Jan. 20, 2000, now Pat. No. 6,274,171, which is a continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** **424/461**; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/461, 458, 424/459, 457, 456, 462, 494, 495

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and fiber provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

14 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application is a continuation of Ser. No. 09/884,412, filed Jun. 19, 2001, which is a a divisional application of Ser. No. 09/488,629, filed Jan. 20, 2000, now U.S. Pat. No. 6,274,171, which is a continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997, now abandoned, which is a continuation-in part of Application No. 08/821,137, filed Mar. 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodin) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be thin-coated to retard dissolution. The fin-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in

doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the -plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride compris-

ing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NT, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A ether preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCT and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a bard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide, the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 -to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such fierier experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>30

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are

filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U.S. Pharmacopoeia (JSP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 am through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 mm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER causule

Time (hours)	75 mg (IR) tablet (q 12 h)	2 × 75 mg (ER) capsules (q 24 hr)	1 × 150 mg (ER) capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 ml portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Superco Supercoil LC-8-DB, 5 cm×4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Kent. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/spheronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

The 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. A method for providing therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150 ng/ml, said formulation containing venlafaxine hydrochloride as the active ingredient.

2. The method of claim 1 wherein the extended release formulation is encapsulated.

3. The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

4. The method of claim 3 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

5. The method of claim 3 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. The method of claim 5 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

7. The method of claim 6 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. The method of claim 3 wherein the spheroids are coated with from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. The method of claim 8 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

10. The method of claim 3 wherein the spheroids are coated with from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. The method of claim 3 wherein the spheroids are coated with from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

12. The method of claim 11 wherein the spheroids are comprised of about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

13. The method of claim 1 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid.

14. The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid.

* * * * *

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For:	Extended Release Formulation		
Confirmation No.:			
Customer Number:	25291		

Assistant Commissioner for Patents
Washington, DC 20231

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In accordance with 37 CFR 1.97 and 1.98, Applicants submit herewith patents, publications, or other information of which they are aware, which they believe may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR 1.56. This Information Disclosure Statement is not to be construed as a representation that: (i) a search has been made; (ii) the information is material to the examination of this application; (iii) additional information material to the examination of this application does not exist; (iv) the information, protocols, results and the like reported by third parties are accurate or enabling; or (v) the information constitutes prior art to the subject invention.

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I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EM474059865USaddressed to the Assistant Commissioner for Patents, Washington, DC 20231.

September 12, 2001
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Mary Ellen Fiala
Mary Ellen Fiala

WYETH 002-000385

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☐ Newly Cited Information
A legible copy of the patents, publications or other information cited on the attached form PTO 1449 is enclosed, except that no copy of a pending U.S. application is enclosed.

☒ Previously Cited Information
No copy of the patents, publications or other information cited on the attached form PTO-1449 is enclosed because it has been previously cited by or submitted to the Office in a prior application which is relied upon for an earlier filing date under 35 USC 120.
Prior application is Serial Number 09/488,620, filed on January 20, 2000 of Sherman et al. for Extended Release Formulation..

WYETH 002-000386

☐ Concise Explanation
Documents cited above which are not in the English Language

a. ☐ have been explained in the specification.
b. ☐ have an abstract (or other concise explanation) in English enclosed or if readily available a translation into English of the document is enclosed.

Form PTO-1449 is enclosed in duplicate.

☐ Fees
☐ Fee for filing under 37 CFR 1.97(c) or (d) Fee: $0.00

Method of Payment of Fees:
Charge American Home Products Corporation Deposit Account No. 01-1425
in the amount of $0.00
A duplicate of this statement is enclosed.

Instructions as to Overpayment/Underpayment:
Credit any overpayment and charge any underpayment to Deposit Account No. 01-1425.

Rebecca R. Barrett

Rebecca R. Barrett
Reg. No. 35,152

American Home Products Corporation
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2646

File Copy

FORM PTO-1449 (REV. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. AHP-95011- C1	SERIAL NO. Not Yet Known
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Deborah M. Sherman et al.	
	FILING DATE Not Yet Known	GROUP 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	3 9 5 4 9 5 9	~~8/75~~ 5/4/76	Pedersen			
	AB	4 3 6 9 1 7 2	1/83	Schor et al.			
	AC	4 1 3 8 4 7 5	2/79	McAinsh et al.			
	AD	4 3 8 9 3 9 3	6/83	Schor et al.			
	AE	4 9 6 6 7 6 8	10/90	Michelucci et al.			
	AF	5 5 0 6 2 7 0	4/96	Upton et al.			
	AG	4 5 3 5 1 8 6	8/86	Husbands et al.			
	AH	5 5 5 2 4 2 9	9/96	Wong et al.			
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
AL	0 6 5 4 2 6 4	11/94	EP				
AM	0 6 6 7 1 5 0	1/95	EP				
AN	9 4 2 7 5 8 9	12/94	WO				
AO	9 7 3 7 6 4 0	10/97	WO				
AP	0 7 9 7 9 9 1	10/97	EP				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AQ	
AR	
AS	
AT	
AU	
AV	

EXAMINER	DATE CONSIDERED
JAMES M. SPEAR	12-3-2001

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

AHP-95011-C1
PATENT

#3/A
#10
11/5/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark, John U. Lamer, Stephen A. White

Serial No.: (Cont. of USSN 09/884,412)

Examiner:

Filed: Herewith

Group:

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to issuance of an Office Action in this case, please amend the application as follows:

In the Application:

At page 1, line 3, please delete "This application is a divisional application of Serial No. 09/488,629, filed January 20, 2000 which is a continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, now abandoned, which is a continuation-in-part of Application No. 08/821,137, filed March 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed March 25, 1996" and insert -- "This application is a continuation of Serial No. 09/884,412, filed June 19, 2001, which is a a divisional application of Serial No. 09/488,629, filed January 20, 2000, which is a continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, now abandoned, which is a continuation-in-part of Application No. 08/821,137, filed March 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed March 25, 1996. --

In the Claims:

Cancel Claims 2-22 without prejudice.

Add new Claims 23-34 as follows:

--23. A method for providing therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150ng/ml, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. The method of Claim 1 wherein the extended release formulation is encapsulated.

25. The method of Claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

26. The method of Claim ~~25~~ 3 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

27. The method of Claim ~~25~~ 3 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

28. The method of Claim ~~27~~ 5 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

29. The method of Claim ~~28~~ 6 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8 ~~30.~~ The method of Claim ~~25~~ 3 wherein the spheroids are coated with from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose,

9 ~~31.~~ The method of Claim ~~30~~ 8 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

10 ~~32.~~ The method of Claim ~~25~~ 3 wherein the spheroids are coated with from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11 ~~33.~~ The method of Claim ~~25~~ 3 wherein the spheroids are coated with from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

12 ~~34.~~ The method of Claim ~~33~~ 11 wherein the spheroids are comprised of about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. - -

In view of the foregoing, Applicants respectfully maintain that Claims 1 and 23-34 are in condition ready for allowance and respectfully request an early and favorable Notice of Allowance.

Respectfully submitted,

Rebecca R. Barrett

Rebecca R. Barrett
Reg. No. 35,152

Dated: September 12, 2001
Telephone: (610) 902-2646

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,965	09/12/2001	Deborah M. Sherman	AHP-95011 C1	2886

25291 7590 12/05/2001

AMERICAN HOME PRODUCTS CORPORATION
FIVE GIRALDA FARMS
PATENT LAW
MADISON, NJ 07940

EXAMINER	
SPEAR, JAMES M	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary

Application No.	Applicant(s)
09/950,965	SHERMAN, ET AL
Examiner	**Art Unit**
JAMES M. SPEAR	1615

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 12, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 23-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *23* is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☒ Claim(s) *24-34* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are dependent claims which depend on a method, however claims 24 and 25 depend on claim 1 which is a product/composition claim..

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al US 4,138,475 in view of Wong et al US 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to formulate the core spheroid. See Abstract, example and claim 1. The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art. It would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in the McAinsh sustained release dosage form to increase patient compliance when the need arises to administer both drugs. The motivation being a desire to obtain

optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required. It is also reasonable to expect that one may choose to use the same sustained release formulation for either drug alone in a single dosage form for those times when only venlafaxine or propranolol is required to be administered as a sustained/extended release formulation. The goal being to obtain optimum release profiles.

Claim 23 is allowed.

Claims 2-22 have been canceled. Claims 24-34 are objected to. Claim 1 is rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308 2457. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305 3592 or 308 4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308 1235.

James Spear

December 3, 2001

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

05-06-02 1615

Docket No: AHP-95011C1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	Deborah M. SHERMAN, et al.		
Serial No.:	09/950,965	Group Art No.:	1615
Filed:	September 12, 2001	Examiner:	James M. Spear
For:	Extended Release Formulation		
Confirmation No.:	2886		
Customer Number:	25291		

Commissioner for Patents
Washington, DC 20231

Sir:

AMENDMENT TRANSMITTAL LETTER

1. Enclosed please find the following documents for the above-identified application:

Response to Office Action mailed on December 5, 2001

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number ET302331224US" addressed to the Commissioner for Patents, Washington, DC 20231.

March 5, 2002
Date

Bubinea D. Owens
Bubinea D. Owens

WYETH 002-000411

cket No: AHP-95011C1
Patent

2. Fee calculation

CLAIMS AS AMENDED					
(1) FOR	(2) CLAIMS REMAINING AFTER AMENDMENT	(3) HIGHEST NUMBER PAID FOR	(4) NUMBER EXTRA x RATE		(5) ADDITIONAL FEE
TOTAL CLAIMS	14	20	0	x $ 18.00	0.00
INDEPENDENT CLAIMS	1	3	0	x $ 84.00	0.00
MULTIPLE DEPENDENCY FEE				$ 280.00	
			Total Amendment Fee:		$0.00

☒ Please charge Deposit Account No. 01-1425 for: $0.00

The Commissioner is hereby authorized to charge any additional fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account No. 01-1425. A copy of this letter is enclosed for use by the Deposit Account Branch.

Respectfully submitted,

Rebecca R. Barrett

Rebecca R. Barrett
Attorney for Applicants
Reg. No. 35,152

American Home Products Corporation
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2646

WYETH 002-000412

ocket No: AHP-95011C1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Deborah M. SHERMAN, et al.		
Serial No.:	09/950,965	Group Art No.:	1615
Filed:	September 12, 2001	Examiner:	James M. Spear
For:	Extended Release Formulation		
Confirmation No.:	2886		
Customer Number:	25291		

Commissioner for Patents
Washington, DC 20231

Sir:

AMENDMENT TRANSMITTAL LETTER

1. Enclosed please find the following documents for the above-identified application:

Response to Office Action mailed on December 5, 2001

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number ET302331224US" addressed to the Commissioner for Patents, Washington, DC 20231.

March 5, 2002 — Bubinea D. Owens
Date — Bubinea D. Owens

2. Fee calculation

CLAIMS AS AMENDED					
(1) FOR	(2) CLAIMS REMAINING AFTER AMENDMENT	(3) HIGHEST NUMBER PAID FOR	(4) NUMBER EXTRA x RATE		(5) ADDITIONAL FEE
TOTAL CLAIMS	14	20	0	x $ 18.00	0.00
INDEPENDENT CLAIMS	1	3	0	x $ 84.00	0.00
MULTIPLE DEPENDENCY FEE				$ 280.00	
			Total Amendment Fee:		$0.00

☒ Please charge Deposit Account No. 01-1425 for: $0.00

The Commissioner is hereby authorized to charge any additional fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account No. 01-1425. A copy of this letter is enclosed for use by the Deposit Account Branch.

Respectfully submitted,

Rebecca R. Barrett

Rebecca R. Barrett
Attorney for Applicants
Reg. No. 35,152

American Home Products Corporation
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2646

#43B

Docket No: AHP-95011 C1
Patent
3/16/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	Deborah M. SHERMAN, John C. CLARK, John U. LAMER, Stephen A. WHITE		
Serial No.:	09/950,965	Group No.:	1615
Filed:	September 12, 2001	Examiner:	James M. Spear
For:	Extended Release Formulation		
Confirmation No.:	2886		
Customer Number:	25291		

Commissioner for Patents
Washington, DC 20231

AMENDMENT UNDER 37 C.F.R. §1.111

Sir:

This is in response to the Office Action issued in connection with this case on December 5, 2001. The Office Action has been carefully reviewed and the following response prepared. Please amend the application as follows:

In the Claims:

2 ~~24.~~ (Amended) The method of Claim ~~23~~ 1 wherein the extended release formulation is encapsulated.

B1 3 ~~25.~~ (Amended) The method of Claim ~~23~~ 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

Please add the following new claims:

B2 13 ~~35.~~ The method of Claim ~~23~~ 1 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid.

14 ~~36.~~ The method of Claim ~~23~~ 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid.

Please cancel Claim 1, without prejudice.

Remarks

Claims 1 and 23-34 were pending in this application. Claim 1 was cancelled, without prejudice. New Claims 35 and 36 were added to more fully claim subject matter of the claimed invention. Claim 1 was rejected. Claims 24-34 were objected to. Applicants appreciate the Examiner's indication that Claim 23 is allowed.

Claims 24-34 were objected to as being of inproper dependent form. Applicants have amended the dependencies of claims 24 and 25 to depend from Claim 23. Claims 24-34 now properly depend, directly or indirectly, from Claim 23. Accordingly the dependencies have been corrected and this objection should be withdrawn.

Claims 35 and 36 were added to more fully claim the subject matter of the invention. No new matter was added by this amendment.

Claim 1 was rejected under §103(a). To facilitate prosecution of this application, Claim 1 was cancelled, without prejudice, making this rejection moot.

In view of the foregoing, Applicants respectfully maintain that Claims 23-36 are in condition ready for allowance and respectfully request an early and favorable Notice of Allowance.

Respectfully submitted,

Rebecca R. Barrett
Reg. No. 35, 152
Attorney for Applicants

Dated: March 5, 2002
Telephone: (610) 902-2646

Marked Up Copy of Amended Claims

24. The method of Claim [1] 23 wherein the extended release formulation is encapsulated.

25. The method of Claim [1] 23 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

Please add the following new claims:

--35. The method of Claim 23 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid.

36. The method of Claim 23 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid. --

Notice of Allowability

Application No.	Applicant(s)
09/950,965	SHERMAN, ET AL
Examiner	**Art Unit**
JAMES M. SPEAR	1615

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *THE AMENDMENT FILED MARCH 05, 2002*.
2. ☒ The allowed claim(s) is/are *23-36*.
3. ☐ The drawings filed on _____ are acceptable as formal drawings.
4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____.
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   *Certified copies not received: _____.
5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. _____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.
8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☐ Examiner's Statement of Reasons for Allowance
9 ☐ Other

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

25291 7590 03/19/2002

WYETH
FIVE GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
SPEAR, JAMES M	
ART UNIT	**CLASS-SUBCLASS**
1615	424-439000

DATE MAILED: 03/19/2002

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,965	09/12/2001	Deborah M. Sherman	AHP-95011 C1	2886

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
14	nonprovisional	NO	$1280	$300	$1580	06/19/2002

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PTOL-85 (REV. 07-01) Approved for use through 01/31/2004.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,965	09/12/2001	Deborah M. Sherman	AHP-95011 C1	2886

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
14	nonprovisional	NO	$1280	$300	$1580	06/19/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPEAR, JAMES M	1615	424-439000

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,965	09/12/2001	Deborah M. Sherman	AHP-95011 C1	2886

EXAMINER
SPEAR, JAMES M

ART UNIT	PAPER NUMBER
1615	

25291 7590 03/19/2002

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DATE MAILED: 03/19/2002

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(application filed on or after May 29, 2000)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,965	09/12/2001	Deborah M. Sherman	AHP-95011 C1	2885

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
14	nonprovisional	NO	$1280	$300	$1580	06/19/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPEAR, JAMES M	1615	424-439000

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1 Rebecca R. Barrett
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US006274171B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,274,171 B1**
(45) **Date of Patent: Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: **Deborah M. Sherman**, Plattsburgh; **John C. Clark**, Peru, both of NY (US); **John U. Lamer**, St. Albans, VT (US); **Steven A. White**, Champlain, NY (US)

(73) Assignee: **American Home Products Corporation**, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/488,629**

(22) Filed: **Jan. 20, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] A61K 9/52; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** 424/461; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/495, 494, 424/461, 458, 459, 457, 456, 462

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,954,959	5/1976	Pedersen	424/21
4,138,475 *	2/1979	McAinsh et al.	424/19
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* cited by examiner

Primary Examiner—James M. Spear
(74) *Attorney, Agent, or Firm*—Rebecca R. Barrett

(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

25 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine ls hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloric is polymorphic. Of the forms

isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1- 4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl Released
2	...50
4	30-55
8	55-80
12	to 90
24	...80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	133.6	53.3	53.2
2	212.1	69.8	70.9
4	164.9	138.6	133.3
6	111.6	149.0	143.5
8	86.1	129.3	129.5
10		118.4	114.3
12	51.9	105.1	105.8
12.5	71.7		
13	127.2		
14	161.3	90.5	91.3
16	132.6	78.2	78.5
18	86.1		

TABLE 2-continued

Plasma venlafaxine level (ng/ml.) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4. hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.58	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.83	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.5	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −30° C. until analysis could be completed.

To 1 mL. of each plasma sample in a plastic tube was added 150 μl of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 ml. portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μl. samples were injected on a Supelco Supelcoil LC-8-DB, 5 cmx4.6 mm, 5 μ, column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model

FM 6E-Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/spheronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 60% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	≤30
4	30–55
8	55–80
12	65–90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6–8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0–51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0–51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0–51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.:

Time	Average % Venlafaxine HCl Released
2	≤30
4	30–55
8	55–80
12	65–90
24	>80

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof,

an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

* * * * *

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2000

Application or Docket Number: AHP-95011 C1

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	12	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	12 minus 20=	* 0
INDEPENDENT CLAIMS	1 minus 3 =	* 0
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	355.00	OR	BASIC FEE	710.00
X$ 9=		OR	X$18=	—
X40=		OR	X80=	—
+135=		OR	+270=	—
TOTAL		OR	TOTAL	710

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 14	Minus	**	= 0
Independent	* 1	Minus	***	= 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

CLAIMS ONLY

SERIAL NO.

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT		*		*		*	
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TOTAL DEP.						
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

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(54) **EXTENDED RELEASE FORMULATION**

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and fiber provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

EXTENDED RELEASE FORMULATION

[0001] This application continuation-in-part of application Ser. No. 08/964,328, filed Nov. 5, 1997, which is a continuation-in-part of copending application Ser. No. 08/821,137, filed Mar. 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

[0002] Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage, form of the analgesic/anti-inflammatory drug etodolac (Lodin) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

[0003] Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be thin-coated to retard dissolution. The fin-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

[0004] Venlafaxine, 1-[2-(dimethylamino)-1-(4methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. La therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiting additional dosing with the drug. With the plural daily dosing regimen the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

[0005] In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

[0006] Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the -plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

[0007] The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

[0008] The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

[0009] More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

[0010] A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NT, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

[0011] Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

[0012] Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A ether preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCT and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present Each of these formulations is also preferably contained in a gelatin capsule, preferably a bard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

[0013] 1-[2-(dimethylamino)-1-(4methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

[0014] The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide, the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

[0015] The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon HG 2834.

[0016] Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are

preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55° C.

[0017] It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

[0018] Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 -to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

[0019] The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

[0020] The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

[0021] The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

[0022] Venlafaxine Hydrochloride Extended Release Capsules

[0023] A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

[0024] Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

[0025] To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

[0026] The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

[0027] Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

[0028] Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

[0029] Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

[0030] In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

[0031] In such fierier experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

[0032] Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

[0033] Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

[0034] The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

[0035] Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>30

[0036] Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

[0037] Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U.S. Pharmacopoeia (JSP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 am through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 mm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

[0038] The percentage of venlafaxine released is determined from the equation

$$\%\ \text{Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

[0039] where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

[0040] Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR) tablet (q 12 h)	2 × 75 mg (ER) capsules (q 24 hr)	1 × 150 mg (ER) capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

[0041] Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

[0042] Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

[0043] Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formu-

lated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

[0044] The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −20° C. until analysis could be completed.

[0045] To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 ml portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supercо Supercoil LC-8-DB, 5 cmx4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

[0046] Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

[0047] Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

[0048] These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

[0049] The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

[0050] Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Kent. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/spheronization machine (Aromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcelluose, 2910 USP, 6 cps	0.675

[0051] The 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

[0052] A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

[0053] Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 6 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

12. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

13. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. A composition according to claim 2 wherein the film coating comprises 6-8% by weight of total weight.

15. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. A composition according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

17. A film coating composition according to claim 2 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. A film coating composition according to claim 2 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropylmethylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

20. An extended release formulation of venlafaxine hydrochloride according to claim 2 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

21. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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Assignments
Examiner Number: 68484 / SPEAR, JAMES
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Status: 150 / PATENTED CASE
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Title of Invention: EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

Bar Code	Location	Location Date	Chrg to Loc	Charge to Name	Emp. ID	Infra Loc
09488629	9200	12/03/2001	9210	No Charge to Name	DDAVIS6	

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | Invent

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WYETH 002-000442

WEST

Freeform Search

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Term: 12 and (venlafaxine same capsule)

Display: 10 **Documents in Display Format:** CIT **Starting with Number** 1

Generate: ○ Hit List ◉ Hit Count ○ Image

Search | Clear | Help | Logout | Interrupt

Main Menu | Show S Numbers | Edit S Numbers | Preferences

Search History

Today's Date: 12/3/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l2 and (venlafaxine same capsule)	13	L4
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l2 and (venlafaxine same capsule same release)	3	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l1 and capsule	118	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	VENLAFAXINE	171	L1

WEST Search History

DATE: Monday, March 18, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=AND			
L5	(venlafaxine same sustained adj release)	6	L5
L4	(venlafaxine same controlled adj release)	2	L4
L3	(dimethylamino same methoxyphenyl same cyclohexanol)	58	L3
L2	(dimethylamino same methochphenyl same cyclohexanol)	0	L2
L1	venlafaxine same (extended adj release)	8	L1

END OF SEARCH HISTORY

ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION	JJR		09-14-01
O.I.P.E. CLASSIFIER			
FORMALITY REVIEW	BZ	897	10-10-01
RESPONSE FORMALITY REVIEW			

INDEX OF CLAIMS

✔ ..... Rejected
= ..... Allowed
— (Through numeral)... Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim Final	Claim Original	Date
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SEARCHED

Class	Sub.	Date	Exmr.
424	461	12-3-01	JSpear
	458	"	
	459	"	
	457	"	
	456	"	
	462	"	
	494	"	
	495	"	
Above to Date		3-18-02	JSpear

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

	Date	Exmr.
WEST 2.0	12-3-01	JSpear
"	3-18-02	JSpear

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
424	461	3-18-02	JSpear
	458	"	
	459		
	457		
	456		
	462		
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	495		

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WYETH 002-000446

CONTENTS

	Date Received (Incl. C. of M.) or Date Mailed		Date Received (Incl. C. of M.) or Date Mailed
1. Application ✓ papers.		42.	
2. IDS	9-12-01	43.	
3. Trans Amdt A	9-12-01	44.	
4. Restriction (3mo)	12-5-01	45.	
5. Amdt B	03-05-02	46.	
6. Allowance	8/14/02	47.	
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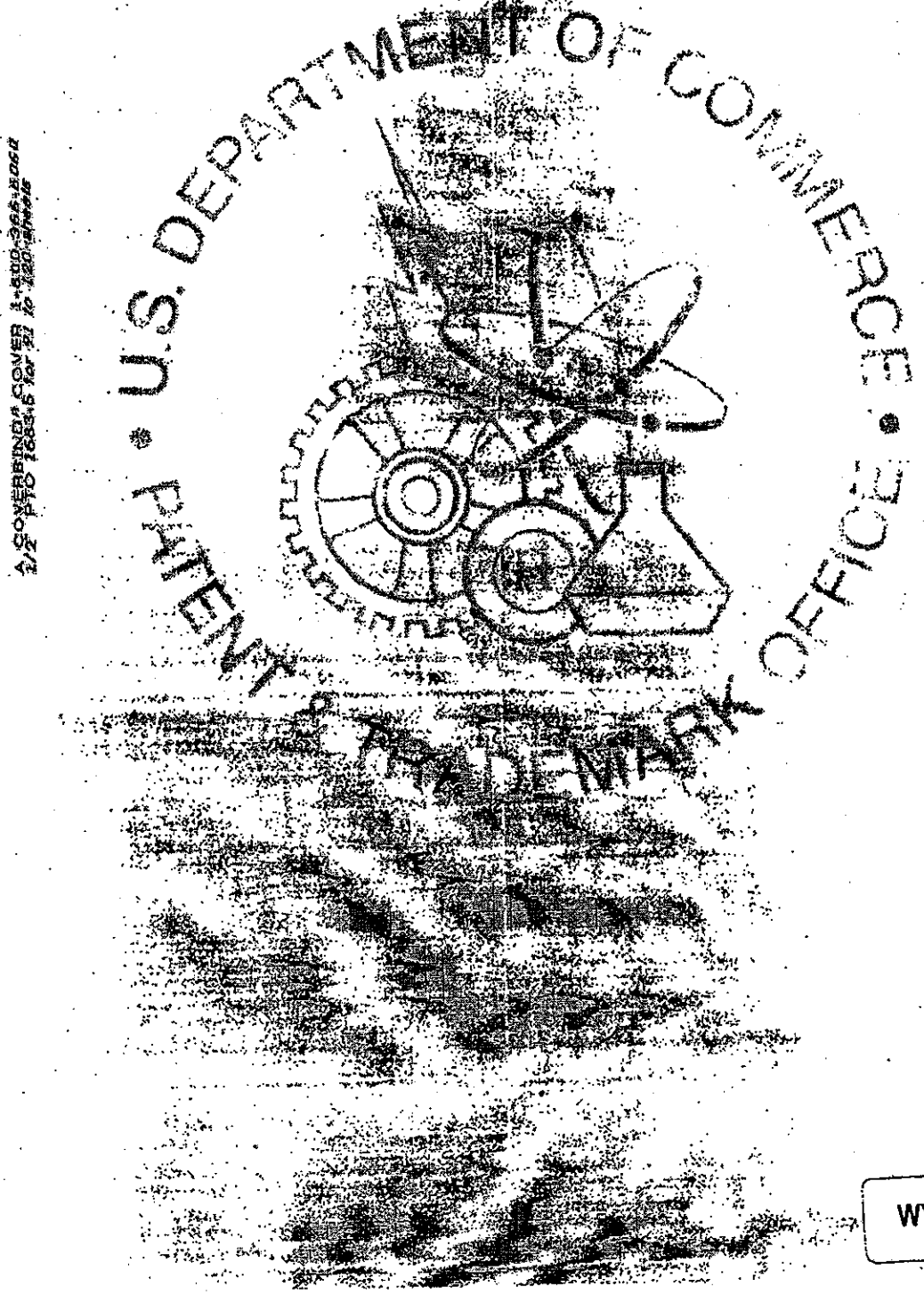

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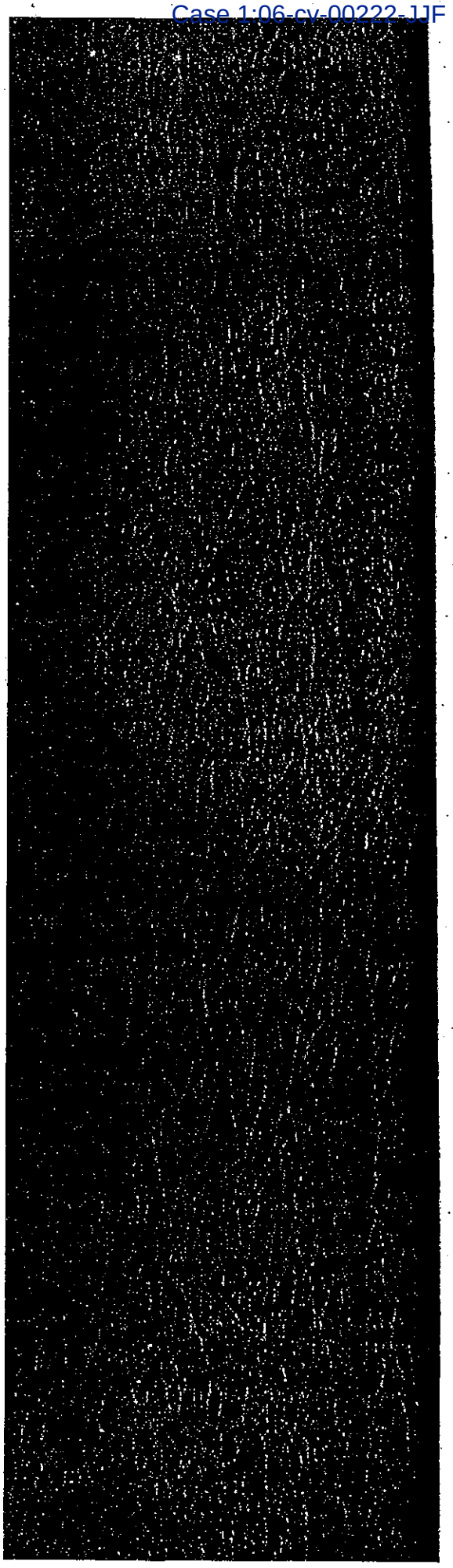

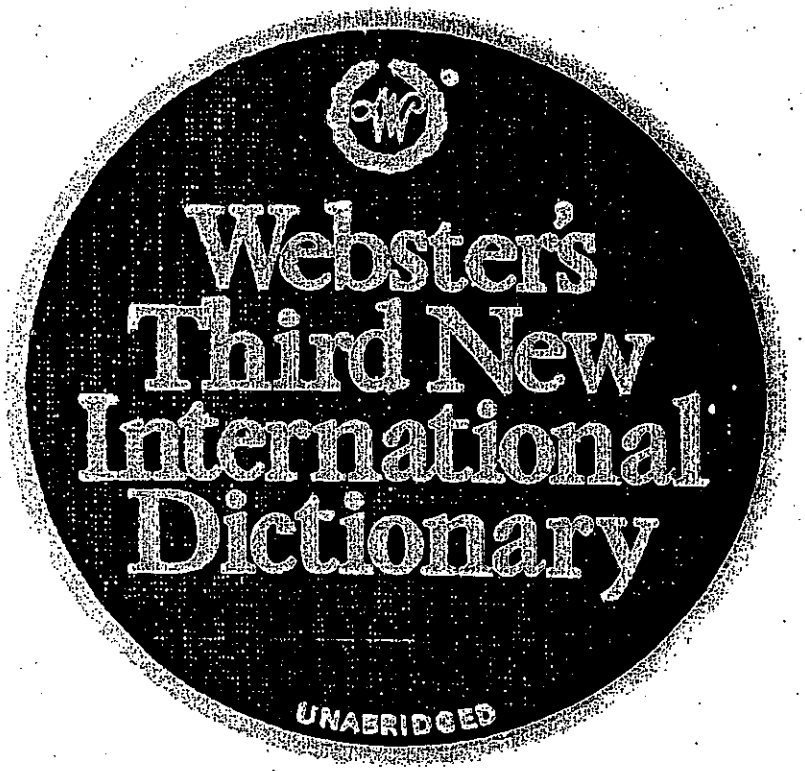
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or with difficulty ⟨a ~ awareness of his environment⟩ : indistinctly known or remembered ⟨the ~ centuries of the later empire —Roger Fry⟩ : sensed or perceived weakly in an emotional or intuitional manner ⟨led . . . early man to a ~ feeling for symbolism —Edward Sapir⟩ : of a hazy or indefinite nature ⟨claimed some ~ relationship with Houdini —R.G.G. Price⟩ d : having little prospect of favorable result or outcome ⟨a ~ future⟩ : unlikely to be fulfilled or realized ⟨the ~ expectancy that he might return —Ann Ryan⟩ e : characterized by an unfavorable, skeptical, pessimistic, disapproving, or unenthusiastic attitude — usu. used in the phrase *take a dim view of* ⟨he takes a ~ view of human nature⟩ ⟨the villagers take a ~ view of people who try to impress them⟩ 3 a : not perceiving clearly and distinctly with one of the senses (as sight) ⟨eyes grown ~ with age⟩ b : dull and weak in understanding or comprehension ⟨big and overdeveloped and ~ in her wits —Louis Bromfield⟩ syn see DARK

²dim \"\ *vb* **dimmed; dimmed; dimming; dims** [ME *dimmen*, fr. *dim*, adj.] *vt* **1** : to make dim ⟨~ the theater lights⟩ ⟨the years could not ~ his early love⟩ ⟨the incident *dimmed* the prospects for peace⟩ **2** : to reduce the light from (headlights) by switching to the low beam ~ *vi* : to become dim ⟨her fame and beauty *dimmed* rapidly⟩ ⟨the way the lights ~ in a farmhouse during a storm —John Cheever⟩ syn see OBSCURE

³dim \"\ *n* -s **1** *archaic* : DIMNESS, DUSK **2 a** : PARKING LIGHT ⟨put his lights on the ~ and pulled into the curb —Erle Stanley Gardner⟩ **b** : LOW BEAM

dim *abbr* **1** dimension **2** [L *dimidium*] half **3** diminished **4** diminuendo **5** diminutive

dim-ble \'dim(b)əl\ *n* -s [perh. alter. of *dingle*] *dial Eng* : a ravine with a watercourse : DINGLE

dime \'dīm\ *n* -s [ME, fr. MF *dime, disme*, fr. L *decima*, fr. fem. of *decimus* tenth (adj.), fr. *decem* ten — more at TEN] **1** *archaic* : a tenth or tithe **2 a** : a coin of the U.S. first issued in 1796 and worth ⅒ dollar **b** : the sum of ten cents ⟨the price of admission was only a ~⟩ **c** dimes *pl, archaic* : money or financial gain ⟨no matter about her temper — has she got the ~s —Mary J. Holmes⟩ **d** : a petty sum of money ⟨they made hardly a ~⟩ ⟨they hadn't lost a ~ on the deal —Nelson Algren⟩ **3** : a Canadian ten-cent piece — **a dime a dozen** : plentiful or commonplace to the point of having little value ⟨heroes were *a dime a dozen* that day —*Infantry Jour.*⟩ — **on a dime** *adv* : in a very small area ⟨this car can turn *on a dime*⟩ : INSTANTLY ⟨stopped *on a dime*⟩

dime-don \'dīmə,dän, *or* **di-me-done** \-,dōn\ *n* -s [*dime-* (fr. *dimethyl*) + *-d-* (fr. *dihydr-*) + *-one*] : a crystalline diketone $C_9H_{12}O_2$ made by reaction of mesityl oxide and ethyl malonate and used in the analysis of aldehydes with which it forms insoluble derivatives; 5,5-dimethyl-1,3-cyclohexanedione

dime museum *n* : a collection of often lurid and sensational curiosities, monstrosities, and freaks exhibited for a low price of admission

di-men-hy-dri-nate \,dī,men'hīdrə,nāt\ *n* -s [*dime-* (fr. *dimethyl*) + *-n-* (fr. *amine*) + *-hydrin-* (fr. *diphenhydramine*) + *-ate*] : a crystalline compound $C_{29}H_{33}NO_5C_7H_7ClN_4O_2$ made by reaction of diphenhydramine with 8-chloro-theophylline and used in the prevention or treatment of motion sickness and postoperative nausea

dime novel *n* : an inexpensive paper-bound melodramatic novel of adventure popular in the U.S. from about 1860 to World War I — compare ³DREADFUL **2** : a cheap sensational and often lurid novel

¹di-men-sion \də'menchən *sometimes* dī'-\ *n* -s *often attrib* [ME *dimensioun*, fr. MF *dimension*, fr. L *dimension-, dimensio*, fr. *dimensus* (past part. of *dimetiri* to measure out, fr. *di-* — fr. *dis-* apart — + *metiri* to measure) + *-ion-, -io* -ion — more at DIS-, MEASURE] **1 a** : measure in a single line (as length, breadth, height, thickness, or circumference) ; one of the three coordinates of position; *specif* : the physical characteristic of length, breadth, or thickness ⟨a line has one ~ (length), a plane has two ~s (length and breadth), and a cube has three ~s (length, breadth, and thickness)⟩ — usu. used in pl. **b** : the quality of spatial extension ⟨~ is a common trait of all matter⟩ : MAGNITUDE, SIZE ⟨the town's modest ~s and leisurely ways —Jane Shellhase⟩ **c** (1) : the range over which or the degree to which something extends : EXTENT, SCOPE, PROPORTIONS ⟨the vast ~s of the disaster⟩ ⟨music grown to the ~s of a great art⟩ — usu. used in pl. (2) : the quality, character, or moral or intellectual stature proper to or belonging to a person (reduced to his own natural ~s —J.G.Lockhart⟩ — usu. used in pl. (3) *chiefly in literature and art* : lifelike or realistic quality ⟨a portrayal from which the character of Hamlet emerges bloodless, without ~⟩ : largeness of vision or thought ⟨reasoned convictions give his work a ~ lacking in the plays of lesser men⟩ **d** (1) : the particular set of circumstances or environmental factors within which someone or something exists or with reference to which something is viewed ⟨for a social novelist . . . time is the ~ in which his materials exist —Granville Hicks⟩ (2) : one of the elements or factors making up a complete personality or entity ⟨no other character in the book has more than one ~⟩ : one of the planes of organization or one of the aspects of a cultural phenomenon ⟨every human situation has environmental, organic, and social ~s⟩ ⟨preoccupation with geography at the expense of other ~s of dialectal diversity —Glenna R. Pickford⟩ : an independent variable or a combination of variables ⟨a psychological test measuring ~s of personality⟩ : QUALITY, ASPECT, TRAIT **2** *archaic* : the act or an instance of measuring : MEASUREMENT **3** *obs* : bodily form or proportions ⟨hath not a Jew hands, organs, ~s? —Shak.⟩ **4** : one of a set of coordinates containing the number of coordinates necessary and sufficient to distinguish any one of the elements of a magnitude or aggregate from all others ; one of the three coordinates of momentum **5** : one of the fundamental units or powers thereof that enter into the makeup of a derived unit ⟨the gram, the square of the centimeter, and the −2 power of the second are the ~s of the erg⟩ **6** : wood or lumber cut to pieces of specified size; as **a** : yard lumber usu. over two inches and under five inches thick and of any width **b** : hardwood in small squares of varying length and thickness for the use esp. of manufacturers of furniture **c** : blocks or slabs of natural stone used chiefly for the construction of masonry walls and memorials syn see SIZE

²dimension \"\ *vt* **dimensioned; dimensioned; dimensioning** \-ch(ə)niŋ\ **dimensions 1** : to make or form (as by cutting or planing) to the required dimensions ⟨the shaft is ~*ed* to fit any wheel⟩ **2** : to figure with dimensions and sometimes also with tolerances (as an architectural plan or a working drawing) : indicate the dimensions on (a drawing)

di-men-sion-al \-chən°l,-chnəl\ *adj* **1** : of or relating to dimension ⟨the ~ stability of properly set nylon fabrics precludes trouble due to shrinkage —H.R.Mauersberger⟩ **2 a** : having dimension ⟨never matures as a ~ character; he is pasty, bland, faceless —Norman Cousins⟩ **b** : having a specified number of dimensions

dimensional analysis *n* : a method of analysis in which physical quantities are expressed in terms of their fundamental dimensions that is often used when there is not enough information to set up precise equations

di-men-sion-al-i-ty \-,enchə'nalədē\ *n* -ES : the quality or state of having dimension : SIZE, MAGNITUDE ⟨~ is the common attribute of all matter⟩

di-men-sion-al-ly \-'menchən°lē, -chnəlē, -lī\ *adv* : with respect to dimension ⟨glass is a ~ stable material⟩

di-men-sioned \-chənd\ *adj* [*¹dimension* + *-ed*] : having dimension : having a specified number of dimensions ⟨three-*dimensioned*⟩

di-men-sion-less \-nləs\ *adj* : having no dimensions

di-men-sive \-n(t)siv\ *adj* [L *dimensus* (past part. of *dimetiri* to measure out) + E *-ive* — more at ¹DIMENSION] *archaic* : DIMENSIONAL

di-mer \'dīmə(r)\ *n* -s [ISV *di-* + *-mer*] : a compound formed [illegible] as an antidote to lewisite but now used in treating poisoning by compounds of arsenic and heavy metals (as mercury and gold): 2,3-di-mercapto-1-propanol — called also *BAL, British anti-lewisite*

di-mer-ic \(ˌ)dī'merik\ *adj* [*dimerous* + *-ic*] **1** *biol* **a** : consisting of two parts : DIMEROUS (a ~ chromosome⟩ **b** : involving or mediated by two factors ⟨~ inheritance⟩ ⟨a ~ character⟩ **2** [*dimer* + *-ic*] : of or relating to a dimer

di-me-ride \'dīmə,rīd, -rəd\ *n* -s [*dimer* + *-ide*] : DIMER

dim-er-ism \'dimə,rizəm\ *n* -s [ISV *dimerous* + *-ism*] : the quality or state of being dimerous

di-mer-i-za-tion \,dīməri'zāshən\ *n* -s [ISV *dimer* + *-ization*] : the process of dimerizing or the state of being dimerized

di-mer-ize \'dīmə,rīz\ *vb* -ED/-ING/-S [back-formation fr. *dimerization*] : to polymerize to a dimer

dim-er-ous \'dimərəs\ *adj* [NL *dimerus*, fr. L *di-* + NL *-merus* -merous] : consisting of two parts: as **a** *of certain insects* : having the tarsi two-jointed **b** *of flowers* : having two members in each whorl

dimes *pl of* DIME

dime store *n* : FIVE-AND-TEN

dim-e-ter \'dimədə(r)\ *n* [LL *dimeter, dimetrus*, n., dimeter, *dimeter, dimetrus*, adj., being a dimeter, fr. Gk *dimetros* being a dimeter, fr. *di-* + *-metros* (fr. *metron* meter, measure) — more at MEASURE] : a line consisting of two metrical feet or of two dipodies

di-me-thoxy- \,dīmə'thäksē, -mē,-\ *comb form* [ISV *di-* + *methoxy-*] : containing two methoxy groups ⟨*dimethoxybenzene* $C_6H_4(OCH_3)_2$⟩

di-methyl \(ˌ)dī+\ *adj* [ISV *di-* + *methyl*] : containing two methyl groups in the molecule

dimethyl-acetylene \(ˌ)dī,methəl+\ *n* [ISV *dimethyl* + *acetylene*] : BUTYNE b

di-meth-yl-amine \(ˌ)dī,methə'lamēn, -thī'lamən\ *n* [ISV *dimethyl* + *amine*] : an easily condensable gaseous compound $(CH_3)_2NH$ having a strong ammoniacal odor made by catalytic reaction of methanol with ammonia or methylamine and used chiefly in organic syntheses (as of vulcanization accelerators for rubber)

dimethylamino- *comb form* [ISV *dimethyl* + *amin-*] : containing the univalent group $(CH_3)_2N-$ derived from dimethylamine ⟨*p-dimethylaminobenzaldehyde*⟩

di-meth-yl-aniline \(ˌ)dī,methəl+\ *n* [ISV *dimethyl* + *aniline*] : a yellowish to brownish oily liquid compound $C_6H_5N(CH_3)_2$ made by methylating aniline and used chiefly as an intermediate (as in dye manufacture)

di-meth-yl-benzene \"+\ *n* [ISV *dimethyl* + *benzene*] : XYLENE 1

dimethyl ether *n* [ISV *dimethyl* + *ether*] **1** : METHYL ETHER 1 **2** : an ether containing two methoxy groups

di-meth-yl-formamide \(ˌ)dī,methəl+\ *n* [*dimethyl* + *formamide*] : a liquid compound $HCON(CH_3)_2$ used esp. at elevated temperatures as solvent for certain polymeric materials in producing synthetic fibers

di-meth-yl-glyoxime \"+\ *n* [ISV *dimethyl* + *glyoxime*] : a crystalline compound $CH_3C(NOH)C(NOH)CH_3$ used as an analytical reagent esp. for precipitating nickel and palladium

dimethyl ketone *n* [ISV *dimethyl* + *ketone*] : ACETONE

di-meth-yl-ol-urea \dī,methə,lōlyù'rēə, -lōl-\ *n* [*dimethyl* + *-ol* + *urea*] : a crystalline compound $CO(NHCH_2OH)_2$ formed as the first stage in making urea-formaldehyde resins and used chiefly in making adhesives and in treating textiles and wood

dimethyl phthalate *n* : a colorless liquid ester $C_6H_4(COOCH_3)_2$ used chiefly as a plasticizer and insect repellent

dimethyl sulfate *n* [ISV *dimethyl* + *sulfate*] : the methyl sulfate $(CH_3)_2SO_4$

di-meth-yl-tubocurarine \(ˌ)dī,methəl+\ *n* : the dimethyl ether of tubocurarine used in the form of a salt (as the chloride $C_{40}H_{44}Cl_2N_2O_6$) as a skeletal muscle relaxant

dimetient *adj* [L *dimetient-, dimetiens*, pres. part. of *dimetiri* to measure out — more at DIMENSION] *obs* : DIAMETRAL

di-metric \(ˌ)dī+\ *adj* [*di-* + Gk *metron* measure + E *-ic*] : tetragonal or hexagonal — compare CRYSTAL SYSTEM

dimetric projection *n* : an axonometric projection in which only two faces are equally inclined to the plane of projection

di-met-ro-don \dī'me-trə,dän\ *n, cap* [NL, fr. *di-* + *metr-* (fr. Gk *metron* measure) + *-odon*] : a genus of No. American Lower Permian synapsid reptiles comprising terrestrial carnivores of moderate size distinguished by a curious crest or dorsal sail supported by greatly elongated neural spines of the vertebrae

dim-i-ca-tion \,dimə'kāshən\ *n* -s [L *dimication-, dimicatio*, fr. *dimicatus* (past part. of *dimicare* to fight, fr. *di-* — fr. *dis-* apart — + *micare* to flash) + *-ion-, -io* -ion; akin to W *dirmygu* to despise, Per *miža, mužo* eyelash, Gk *omichlē* mist — more at DIS-, MIST] *archaic* : CONTEST, STRIFE

¹di-mid-i-ate \də'midē,āt\ *vt* -ED/-ING/-S [L *dimidiatus*, past part. of *dimidiare*] : DIMIDIATE

²di-mid-i-ate \-ēt\ *adj* [L *dimidiatus*, past part. of *dimidiare*] **1** : divided into two equal parts : HALVED **2** *biol* : consisting of only one half of the normal ; seeming to lack one half or to have one part smaller than the other ⟨~ elytra that cover only half the abdomen are common among certain families of beetles⟩

di-mid-i-a-tion \-,midē'āshən\ *n* -s [LL *dimidiation-, dimidiatio* action of halving, fr. L *dimidiatus* + *-ion-, -io* -ion] : a formation of marshaling by joining the dexter half of one heraldic shield with the sinister half of another divided per pale or sometimes per bend

di-min-ish \də'minish, -nēsh, *esp in pres part* -nash\ *vb* -ED/-ING/-ES [ME *deminishen*, alter. (influenced by ME *menusen, minishen* to lessen) of *diminuen*, fr. MF *diminuer*, fr. L *diminuere*, fr. *di-* (fr. *dis-* apart) + *minuere* to lessen — more at DIS-, MINISH, MINOR] *vt* **1** : to make less or cause to appear less : reduce in size, number, or degree ⟨losses and desertions sharply ~*ed* the forces at Washington's disposal⟩ ⟨a tiny figure, rather stooped and ~*ed* by constant ill health —May Sarton⟩ ⟨the passing years did not ~ their friendship⟩ **2** *obs* : to take away or subtract **3** : to lessen the authority, dignity, importance, or reputation of ⟨his society destroyed, his country defeated, his emperor ~*ed* —W.M.Hitzig⟩ ; detract from : DISPARAGE, BELITTLE ⟨began to ~ the skill of the local skaters —S.H.Adams⟩ **4** *archit* : to cause to taper ⟨a ~*ed* column⟩ ~ *vi* **1** : to become less : DWINDLE ⟨his form . . . ~*ed* to a speck on the road —Thomas Hardy⟩ ⟨his interest in the subject had steadily ~*ed*⟩ **2** *archit* : TAPER ⟨a curious tower ~*ing* in five stages to an octagonal cupola⟩ syn see DECREASE

di-min-ish-able \-shəbəl\ *adj* : capable of being diminished

diminished *adj* [fr. past part. of *diminish*] **1** : made less or decreased **2** *of a musical interval* : made one half step less than perfect or minor ⟨a ~ fifth⟩

diminished arch *n* : an arch having less height than half its width (as a segmental or three-centered arch) — compare DROP ARCH

diminished seventh *n* **1** : a chord comprised of three superimposed minor thirds — see SEVENTH CHORD illustration **2** : an interval less by one half step than the minor seventh

diminished shaft *n* : the shaft of a tapering column

diminished triad *or* **diminished chord** *n* : a triad consisting of a minor third and diminished fifth — see TRIAD illustration

di-min-ish-ing-ly *adv* [*diminishing* (pres. part. of *diminish*) + *-ly*] : in a diminishing manner : DECREASINGLY ⟨the rain continued, but ~, all that night⟩

diminishing returns *n pl* : a rate of yield that at a certain point fails to increase in proportion to additional investments of labor or capital — see LAW OF DIMINISHING RETURNS

diminishing rule *n* : a template for contouring a shaft

diminishing stile *n* : a stile that is narrower in one part than in another (as in many glazed doors)

²diminuendo \"\ *n, pl* **diminuendos** *or* **diminuendoes** [It, fr. *diminuendo*, adj.] **1** : a gradual decrease in volume or intensity esp. of sound **2** : a musical passage, phrase, or note played with diminishing volume or force

diminute *adj* [ME *diminut*, fr. L *diminutus*, past part. of *diminuere*] *obs* : DIMINISHED, DIMINUTIVE — **diminutely** *adv, obs*

dim-i-nu-tion \,dimə'n(y)ūshən, -myə'nish-\ *n* -s [ME *diminucioun*, fr. MF *diminution*, fr. L *diminution-, diminutio*, alter. (influenced by L *diminuere* to diminish) of *deminution-, deminutio*, fr. *deminutus* (past part. of *deminuere* to diminish, fr. *de* from, away + *minuere* to lessen) + *-ion-, -io* -ion — more at DE-, MINOR] **1** : the act, process, or an instance of diminishing : DECREASE ⟨experienced no ~ of his physical powers⟩ **2** *archaic* : a lowering in estimation : DEGRADATION, DEPRECIATION **3** : the reduction to smaller note values of the repetition of, imitation of, or answer to a musical subject or phrase — opposed to *augmentation* **4 a** : the defacing of part of a heraldic shield **b** : DIFFERENCE 5 **5** : omission or incompleteness in a record sent up by a lower court in proceedings for review **6** : the tapering or diminishing of a column or some other part of a building; *also* : the amount of such diminishing

di-min-u-ti-val \də,minyə'tīvəl\ *adj* [*diminutive*, n. + *-al*] : ²DIMINUTIVE 1

¹di-min-u-tive \də'minyəd-ləv, -yət\ *n* -s [ME *diminutif*, fr. LL *diminutivum*, alter. (influenced by L *diminuere*) of *deminutivum*, fr. *deminutivus*, adj., fr. L. *deminutus* + *-ivus* -ive] **1** : a diminutive word or affix ⟨*Jeanie* is a ~ of *Jean*⟩ **2** *heraldry* : any of several ordinaries corresponding in characteristic shape and position in the shield with other ordinaries which are greater in width ⟨the bendlet is a ~ of the bend, being one half its width⟩ **3** : a diminutive object or individual ; a small variety or replica ⟨such water flies, ~s of nature —Shak.⟩

²diminutive \"\ *adj* [MF *diminutif*, fr. LL *diminutivus*, alter. (influenced by *diminuere*) of *deminutivus*] **1** : indicating small size and sometimes the quality or condition of being loved, lovable, pitiable, or contemptible — used of affixes (as *-ette, -ie, -kin, -let, -ling, -y*) and of words formed with them (as *kitchenette, Jeanie, lambkin, streamlet, witling, sonny*); contrasted with *augmentative* **2** : small esp. in size : TINY ⟨all was on a ~ scale, like a doll's house⟩ ⟨~ in stature⟩ **3** *archaic* : diminishing or tending to diminish; *also* : DISPARAGING syn see SMALL

di-min-u-tive-ly \-ləvlē, -lī\ *adv* **1** : in a diminutive manner : in a way expressing diminution **2** : to a very small degree : by a very little

di-min-u-tive-ness \-ivnəs\ *n* -ES : extreme smallness or littleness

di-mis-sion \də'mishən, dī'-\ *n* -s [ME, conveyance by lease, fr. ML *dimission-, dimissio*, fr. L. dismissal, discharge, fr. *dimissus* (past part. of *dimittere* to dismiss) +*-ion-, -io* -ion] : dismissal or discharge ⟨a letter of ~⟩

dim-is-so-ri-al \,dimə'sōrēəl, -sȯr-\ *n* -s [NL *dimissorialis* dimissory and commendatory, fr. ML *dimissorius* dimissory and commendatory + L *-alis* -al] : a letter from a pope, bishop, abbot, or other high ecclesiastical official authorizing the ordination of the bearer — called also *dimissory letter*

dim-is-so-ry \'dimə,sōrē, -sȯr-, -ri *sometimes* də'misər- *or* dī'm-\ *adj* [ML *dimissorius* dimissory and commendatory, fr. LL, submitting a matter to a higher court, fr. L *dimissus* (past part. of *dimittere* to dismiss) + *-orius* -ory] : dismissing or granting leave to depart

dimissory letter *n* [trans. of ML *dimissoriae litterae*] **1** : a letter given by a bishop dismissing a clergyman to another diocese and recommending him for reception there **2** : DIMISSORIAL

¹di-mit \də'mit\ *vt* **dimitted; dimitted; dimitting; dimitting** [ME *dimitten* to convey by lease, fr. ML *dimittere*, fr. L, to dismiss, renounce — more at DISMISS] : ¹DEMIT

²dimit *var of* DEMIT

dim-i-ty \'dimədē, -ətē, -ī\ *n* -ES [alter. of ME *demyt*, prob fr. MGk *dimitos* of double thread, fr. LGk, fr. Gk *di-* + *mitos* thread of the warp; perh. akin to Gk *mitra* headband — more at MITER] : a sheer cotton fabric of plain weave that is usu checked or striped by corded effects which are made by weaving two or more threads as one and that is used for clothing and curtains and in a heavier weight for bedspread

dim-ly *adv* [ME, fr. ¹*dim* + *-ly*] : in a dim manner : FAINTLY, INDISTINCTLY, UNCLEARLY ⟨foghorns sounding ~ in the distance⟩ ⟨crooked little side streets, ~ lit by gas lamps —Joh Durant⟩ : VAGUELY, HAZILY, OBSCURELY ⟨only ~ aware of th meaning of these large events⟩

dimmed *past of* DIM

dimmed-ness \'dimədnəs, -m(d)n-\ *n* -ES [*dimmed* (past par of *dim*) + *-ness*] : the quality or state of being dimmed

dimmer *comparative of* DIM

²dim-mer \'dimə(r)\ *n* -s **1** : a device for causing an electr light to burn less brightly (as during a stage play); *esp* : choke coil, rheostat, or transformer connected to the hig **2** dimmers *pl* **a** : PARKING LIGHTS **b** : headlights on lo beam

dimmest *superlative of* DIM

dim-met *or* **dim-mit** \'dimət\ *n* -s [irreg. fr. ¹*dim*] *dial Eng* : TWILIGHT, DUSK

dimming *pres part of* DIM

dim-mish \'dimish\ *adj* : somewhat dim

dim-ness *n* -ES [ME *dimnesse* darkness, obscurity, fr. *dimnes*, fr. *dim* dim, dark + *-nes* -ness] **1** : the quality or sta of being dim **2** : something that is dim

di-molecular \,dī+\ *adj* : BIMOLECULAR

di mol-to \də'mōl(,)tō, dē'-\ *adv* [It] : very much — used a direction in music

di-mo-ric \(ˌ)dī'mȯrik, -mōr-, -mär-\ *adj* [*di-* + *mora* + *-ic* : DISEMIC

di-morph \'dī,mȯrf\ *n* -s [prob. back-formation fr. *dimorphism, dimorphous*] : either of the two crystalline forms o dimorphous substance ⟨calcite and aragonite are ~s⟩

¹di-mor-phic \(ˌ)dī'mȯrfik\ *adj* [*dimorphous* + *-ic*] **1 a** : MORPHOUS 1 **b** : occurring in two distinct forms ⟨~ leaves emergent plants⟩ ⟨a sexually ~ butterfly⟩ **2** : combin qualities of two kinds of individuals in one — used chiefly breeders of fancy-colored canaries

²dimorphic \"\ *n* -s : a dimorphic individual

di-mor-phism \(ˌ)dī'mȯr,fizəm\ *n* -s [ISV *dimorph-* (fr. *dimorphous*) + *-ism*] : the condition or property of be dimorphic or dimorphous; as **a** : difference (as of form, co size) between two individuals or kinds of individuals t might be expected to be similar or identical ⟨the floating submerged leaves of aquatic plants may exhibit considera ~⟩ ⟨in certain marine invertebrates sexual ~ is so extreme t the male is reduced to a minute parasite in the kidney of female⟩ — compare POLYMORPHISM **b** : crystallization in different forms

di-mor-phite \-,fīt\ *n* -s [obs. E *dimorphine* dimorphite It *dimorfina*, fr. *dimorf-* fr. Gk *dimorphos* — + *-ite* -ite] : a mineral As_4S_3 consisting of arsenic sulfide o nally thought to be one of two dimorphous substances

di-mor-pho-the-ca \(ˌ)dī,mȯrfō'thēkə\ *n* [NL, fr. *dimor* (fr. Gk *dimorphos* + *-theca*] **1** *cap* : a genus of south African herbs or subshrubs (family Compositae) with term solitary white, purple, orange, or yellow flower heads sim to those of plants of the genus *Calendula* and with comp ously toothed leaves **2** -s : any plant of the genus *Dimorphot* — called also *African daisy, cape marigold, star of the vel*

di-mor-phous \(ˌ)dī'mȯrfəs\ *adj* [Gk *dimorphos* having forms, fr. *di-* + *-morphos* -morphous] **1** : crystallizing in different forms **2** : DIMORPHIC 1b — **di-mor-phous-ly** *ad*

dim out *vt* : to darken (as a city) by imposition of a dim

dimout \'ˌ\ *n* -s [*dim out*] : a restriction limiting the in lighting or the showing of lights at night esp. during the sh of an air raid; *also* : a condition of partial darkness prod by such restriction ⟨the continuing crisis gradually imp a ~ on the sources and channels of public information⟩ — Lasswell⟩ — compare BLACKOUT

dimple [illegible]

di·min·ish \də'minish, -nësh, *esp in pres part* -nəsh\ *vb* -ED/-ING/-ES [ME *deminishen*, alter. (influenced by ME *menusen*, *minishen* to lessen) of *diminuen*, fr. MF *diminuer*, fr. L *diminuere*, fr. *di-* (fr. *dis-* apart) + *minuere* to lessen — more at DIS-, MINISH, MINOR] *vt* **1** : to make less or cause to appear less : reduce in size, number, or degree ⟨losses and desertions sharply *~ed* the forces at Washington's disposal⟩ ⟨a tiny figure, rather stooped and *~ed* by constant ill health —May Sarton⟩ ⟨the passing years did not ~ their friendship⟩ **2** *obs* : to take away or subtract **3** : to lessen the authority, dignity, importance, or reputation of ⟨his society destroyed, his country defeated, his emperor *~ed* —W.M.Hitzig⟩ : detract from : DISPARAGE, BELITTLE ⟨began to ~ the skill of the local skaters —S.H.Adams⟩ **4** *archit* : to cause to taper ⟨a *~ed* column⟩ ~ *vi* **1** : to become less : DWINDLE ⟨his form . . . *~ed* to a speck on the road —Thomas Hardy⟩ ⟨his interest in the subject had steadily *~ed*⟩ **2** *archit* : TAPER ⟨a curious tower *~ing* in five stages to an octagonal cupola⟩ syn see DECREASE

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EXHIBIT 17

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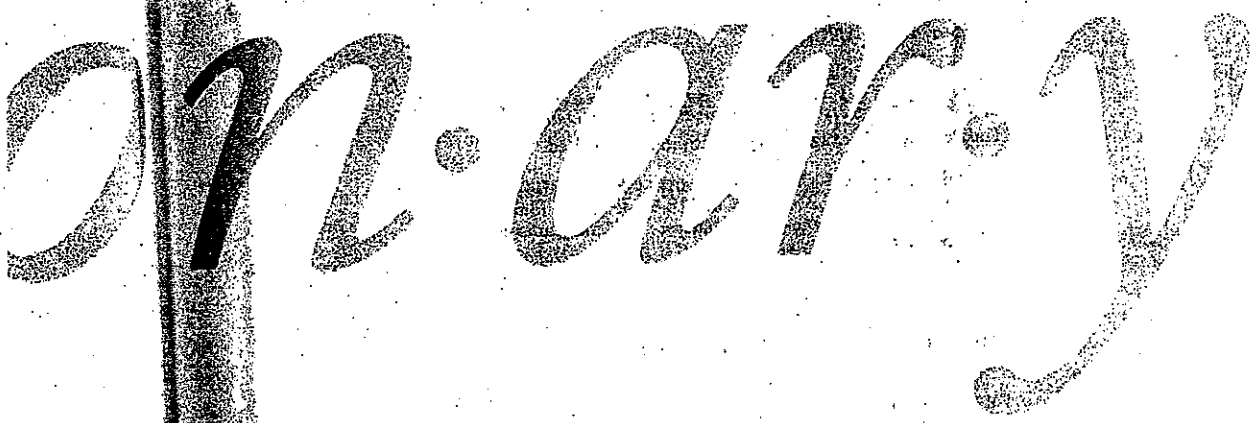
THIRD EDITION



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in•cal•cu•la•ble (ĭn-kăl′kyə-lə-bəl) *adj.* **1.a.** Impossible to calculate: *a mass of incalculable figures.* **b.** Too great to be calculated or reckoned: *incalculable wealth.* **2.** Impossible to foresee; unpredictable. — **in•cal′cu•la•bil′i•ty, in•cal′cu•la•ble•ness** *n.* — **in•cal′cu•la•bly** *adv.*

Syns: incalculable, countless, immeasurable, incomputable, inestimable, infinite, innumerable, measureless. The central meaning shared by these adjectives is "being greater than can be calculated or reckoned": *incalculable riches; countless hours; an immeasurable distance; an incomputable amount; jewels of inestimable value; infinite reasons; innumerable difficulties; measureless power.* Ant: *calculable.*

in•ca•les•cent (ĭn′kə-lĕs′ənt) *adj.* Growing hotter or more ardent. [Lat. *inculēscēns, incalēscent-*, pr.part. of *incalēscere*, to grow warm : *in-*, intensive pref.; see IN-[2] + *calēscere*, to grow warm, inchoative of *calēre*, to be warm; see kelə-[1]*.] — **in′ca•les′cence** *n.*

In cam•er•a (kăm′ər-ə) *adv.* **1.** In secret; privately. **2.** *Law.* In private with a judge rather than in open court. [NLat. *in camerā* : Lat. *in*, in + Med.Lat. *camerā*, chamber.]

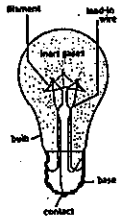
In•can (ĭng′kən) *adj.* Of or relating to the Inca, their civilization, or their language. — *n.* **1.** An Inca. **2.** Quechua.

in•can•desce (ĭn′kən-dĕs′) *tr. & intr.v.* **-desced, -desc•ing, -desc•es.** To make or become incandescent. [Lat. *incandēscere*, to glow : *in-*, intensive pref.; see IN-[2] + *candēscere*, to glow, inchoative of *candēre*, to shine; see kand-*.]

in•can•des•cence (ĭn′kən-dĕs′əns) *n.* **1.** The emission of visible light by a hot object. **2.** The light emitted by such an object. **3.** A high degree of emotion, intensity, or brilliance.

in•can•des•cent (ĭn′kən-dĕs′ənt) *adj.* **1.** Emitting visible light as a result of being heated. **2.** Shining brilliantly; very bright. See Syns at **bright. 3.** Characterized by ardent emotion, intensity, or brilliance. — **in′can•des′cent•ly** *adv.*

incandescent lamp *n.* An electric lamp in which a filament is heated to incandescence by an electric current.



Incandescent lamp

in•can•ta•tion (ĭn′kăn-tā′shən) *n.* **1.** Ritual recitation of charms or spells to produce a magic effect. **2.a.** A formula used in ritual recitation; a charm or spell. **b.** A conventionalized utterance repeated without thought or aptness; a formula. [ME *incantacioun* < OFr. *incantation* < LLat. *incantātiō, incantātiōn-*, spell < Lat. *incantātus*, p.part. of *incantāre*, to enchant. See ENCHANT.] — **in′can•ta′tion•al** *adj.* — **in•can′ta•to′ry** (-tə-tôr′ē, -tōr′ē) *adj.*

in•ca•pa•ble (ĭn-kā′pə-bəl) *adj.* **1.a.** Lacking the necessary ability, capacity, or power: *incapable of love.* **b.** Unable to perform adequately; incompetent. **2.** Not admitting or permitting; not susceptible. **3.** *Law.* Lacking legal qualifications or requirements; ineligible. — **in•ca′pa•bil′i•ty, in•ca′pa•ble•ness** *n.* — **in•ca′pa•bly** *adv.*

in•ca•pac•i•tant (ĭn′kə-păs′ĭ-tənt) *n.* A device or substance, such as tear gas, used to incapacitate individuals temporarily.

in•ca•pac•i•tate (ĭn′kə-păs′ĭ-tāt′) *tr.v.* **-tat•ed, -tat•ing, -tates. 1.** To deprive of strength or ability; disable. **2.** To make legally ineligible; disqualify. — **in′ca•pac′i•ta′tion** *n.*

in•ca•pac•i•ty (ĭn′kə-păs′ĭ-tē) *n., pl.* **-ties. 1.** Inadequate strength or ability; lack of capacity. **2.** A defect or handicap; a disability. **3.** *Law.* Something that renders one incapable.

in•cap•su•late (ĭn-kăp′sə-lāt′) *v.* Var. of **encapsulate.**

in•car•cer•ate (ĭn-kär′sə-rāt′) *tr.v.* **-at•ed, -at•ing, -ates. 1.** To put into jail. **2.** To shut in; confine. [Med.Lat. *incarcerāre, incarcerāt-* : Lat. *in-*, in; see IN-[2] + Lat. *carcer*, prison.] — **in•car′cer•a′tion** *n.* — **in•car′cer•a′tor** *n.*

in•car•na•dine (ĭn-kär′nə-dĭn′, -dēn′, -dīn) *adj.* **1.** Flesh-colored. **2.** Blood-red. — *tr.v.* **-dined, -din•ing, -dines.** To make incarnadine, esp. to redden. [Fr. *incarnadin* < Ital. *incarnatino*, dim. of *incarnato* : *in*, in (< Lat.; see IN-[2]) + *carne*, flesh (< Lat. *carō, carn-*; see INCARNATE).]

in•car•nate (ĭn-kär′nĭt) *adj.* **1.a.** Invested with bodily nature and form: *an incarnate spirit.* **b.** Embodied in human form; personified: *a villain who is evil incarnate.* **2.** Incarnadine. — *tr.v.* (-nāt′) **-nat•ed, -nat•ing, -nates. 1.a.** To give bodily, esp. human, form to. **b.** To personify. **2.** To realize in action or fact; actualize. [ME < LLat. *incarnātus*, p.part. of *incarnāre*, to make flesh : Lat. *in-*, causative pref.; see IN-[2] + Lat. *carō, carn-*, flesh; see sker-[1]*.] — **in•car′na•tor** *n.*

in•car•na•tion (ĭn′kär-nā′shən) *n.* **1.a.** The act of incarnating. **b.** The condition of being incarnated. **2. Incarnation.** *Theol.* The Christian doctrine that the Son of God was conceived in the womb of Mary and that Jesus is true God and true man. **3.** A bodily manifestation of a supernatural being. **4.** One believed to personify a given abstract quality or idea. **5.** A period of time passed in a given bodily form or condition: *hopes for a better life in another incarnation.*

in•case (ĭn-kās′) *v.* Var. of **encase.**

in•cau•tious (ĭn-kô′shəs) *adj.* Not cautious; rash. — **in•cau′tious•ly** *adv.* — **in•cau′tious•ness** *n.*

in•cen•di•ar•y (ĭn-sĕn′dē-ĕr′ē) *adj.* **1.a.** Causing or capable of causing fire. **b.** Of or containing chemicals that produce intensely hot fire when exploded: *an incendiary bomb.* **c.** Of or involving arson. **2.** Tending to inflame; inflammatory. — *n., pl.* **-ies. 1.** An arsonist. **2.** An incendiary device. **3.** One who creates or stirs up factionism or sedition; an agitator. [ME < Lat. *incendiārius* < *incendium*, fire < *incendere*, to set on fire. See INCENSE[1].] — **in•cen′di•a•rism** (-ə-rĭz′əm) *n.*

in•cense[1] (ĭn-sĕns′) *tr.v.* **-censed, -cens•ing, -cens•es.** To cause to be extremely angry; infuriate. [ME *encensen* < OFr. *incenser* < LLat. *incēnsāre*, to sacrifice, burn < Lat. *incēnsus*, p.part. of *incendere*, to set on fire. See kand-*.]

in•cense[2] (ĭn′sĕns′) *n.* **1.a.** An aromatic substance, such as wood or a gum, that is burned to produce a pleasant odor. **b.** The smoke or odor produced by the burning of such a substance. **2.** A pleasant smell. **3.** Flattering or fawning attention; homage. — *tr.v.* **-censed, -cens•ing, -cens•es. 1.** To perfume with incense. **2.** To burn incense to, as a ritual of offering. [ME *encens* < OFr. < Lat. *incēnsum* < neut. p.part. of *incendere*, to set on fire. See kand-*.]

incense cedar *n.* Any of several coniferous evergreen trees of the genera *Calocedrus* and *Libocedrus*, having flattened branches with scalelike leaves.

in•cen•tive (ĭn-sĕn′tĭv) *n.* Something, such as a reward or punishment, that induces action or motivates effort. — *adj.* Serving to induce or motivate. [ME < LLat. *incentīvum* neut. of *incentīvus*, inciting < Lat., setting the tune < *incentus*, p.part. of *incinere*; to sound : *in-*, intensive pref.; see kan- + *canere*, to sing; see kan-*.]

in•cept (ĭn-sĕpt′) *tr.v.* **-cept•ed, -cept•ing, -cepts.** To take in; ingest. [Lat. *incipere, incept-*, to begin, take up. See INCEPTION.] — **in•cep′tor** *n.*

in•cep•tion (ĭn-sĕp′shən) *n.* The beginning of something, such as an undertaking; a commencement. See Syns at **origin.** [ME *incepcion* < Lat. *inceptiō, inceptiōn-* < *inceptus*, p.part. of *incipere*, to begin, take up : *in-*, in; see IN-[2] + *capere*, to take; see kap-*.]

in•cep•tive (ĭn-sĕp′tĭv) *adj.* **1.** Incipient; beginning. **2.** *Gram.* Inchoative. — *n. Gram.* An inchoative verb.

in•cer•ti•tude (ĭn-sûr′tĭ-tōōd′, -työōd′) *n.* **1.** Uncertainty. **2.** Absence of confidence; doubt. **3.** Insecurity or instability.

in•ces•sant (ĭn-sĕs′ənt) *adj.* Continuing without interruption. See Syns at **continual.** [ME *incessaunte* < LLat. *incessāns, incessant-* : Lat. *in-*, not; see IN-[1] + Lat. *cessāns*, pr.part. of *cessāre*, to stop; see CEASE.] — **in•ces′san•cy** *n.* — **in•ces′sant•ly** *adv.*

in•cest (ĭn′sĕst′) *n.* **1.** Sexual relations between persons too closely related that their marriage is illegal or forbidden by custom. **2.** The statutory crime of sexual relations with such a relative. [ME < Lat. *incestum*, neut. of *incestus*, impiure, unchaste : *in-*, not; see IN-[1] + *castus*, pure, chaste; see kes-*.]

in•ces•tu•ous (ĭn-sĕs′chōō-əs) *adj.* **1.** Of, involving, or suggestive of incest. **2.** Having committed incest. **3.** Improperly intimate or interconnected. — **in•ces′tu•ous•ly** *adv.* — **in•ces′tu•ous•ness** *n.*

inch[1] (ĭnch) *n.* **1.** A unit of length in the U.S. Customary and British Imperial systems, equal to 1/12 of a foot (2.54 centimeters). See table at **measurement. 2.** A fall, as of rain or snow, sufficient to cover a surface to the depth of one inch. **3.** A unit of atmospheric pressure that is equal to the pressure exerted by a one-inch column of mercury at the earth's surface at a temperature of 0°C. **4.** A very small degree or amount. — *intr. & tr.v.* **inched, inch•ing, inch•es.** To move or cause to move slowly or by small degrees. — *Idioms.* **every inch.** In every respect; entirely. **inch by inch.** Very gradually; slowly. **within an inch of.** Almost to the point of. [ME < *ynce* < Lat. *uncia*, one twelfth of a unit. See oi-no-*.]

inch[2] (ĭnch) *n. Scots.* A small island. [ME < Sc.Gael. *innis*, Olr. *inis*.]

inch•er (ĭn′chər) *n.* Something measuring a specified number of inches. Often used in combination: *an 18-incher.*

inch•meal (ĭnch′mēl′) *adv.* Little by little; gradually. [INCH[1] (PIECE)MEAL.]

in•cho•ate (ĭn-kō′ĭt) *adj.* **1.** In an initial or early stage of existence; incipient. **2.** Imperfectly formed or developed; *a vague, inchoate idea.* [Lat. *inchoātus*, p.part. of *inchoāre*, to begin, alteration of *incohāre* : *in-*, in; see IN-[2] + *cohum*, strap from yoke to harness.] — **in•cho′ate•ly** *adv.* — **in•cho′ate•ness** *n.*

in•cho•a•tive (ĭn-kō′ə-tĭv) *adj.* **1.** Beginning; initial. **2.** *Gram.* Of or being a verb or verbal form that designates the beginning of an action, a state, or an event. — **in•cho′a•tive•ly** *adv.*

in•chon (ĭn′chŏn′). A city of NW South Korea on an inlet of the Yellow Sea SW of Seoul. Pop. 1,387,000.

inch•worm (ĭnch′wûrm′) *n.* See **measuring worm.**

in•ci•dence (ĭn′sĭ-dəns) *n.* **1.** The act or an instance of happening; occurrence. **2.** Extent or frequency of occurrence: *high incidence of malaria.* **3.** *Phys.* **a.** The arrival of radiation or a projectile at a surface. **b.** Angle of incidence.

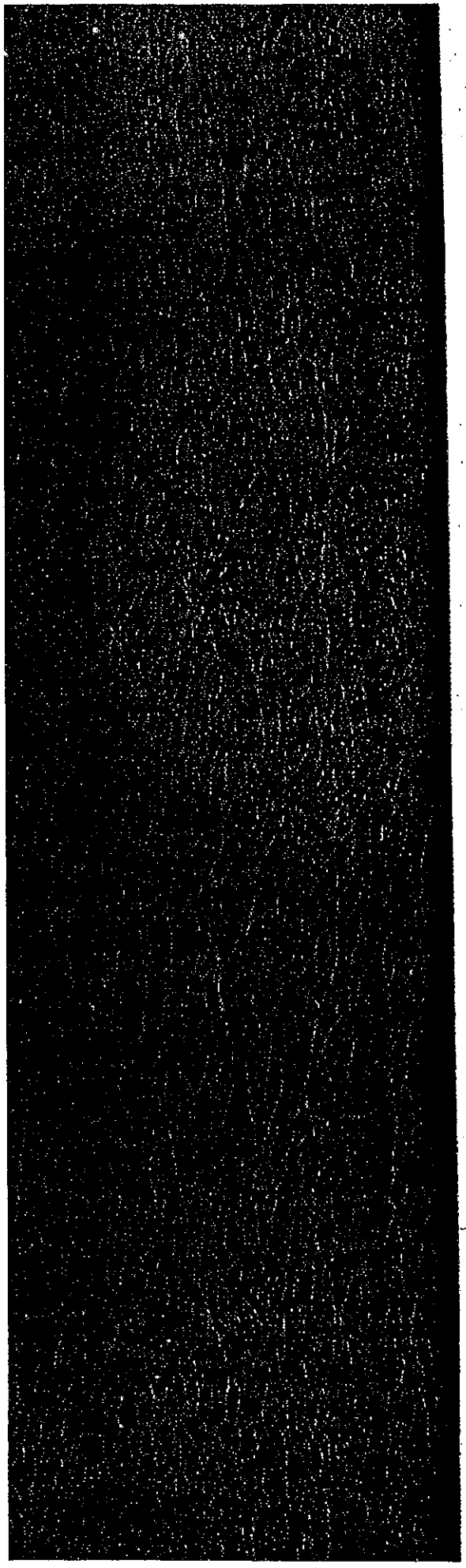
in•ci•dent (ĭn′sĭ-dənt) *n.* **1.** A definite and separate occurrence; an event. See Syns at **occurrence. 2.** A usu. minor action or condition subordinate to another. **3.** Something connected with or related to something else. **4.** An occurrence or episode that interrupts normal procedure or precipitates a crisis: *an international incident.* — *adj.* **1.** Tending to arise or occur as a result or an accompaniment. **2.** Related to or dependent on another thing. **3.** *Phys.* Falling upon or striking a surface: *incident radiation.* [ME < OFr., apt to happen, an incident

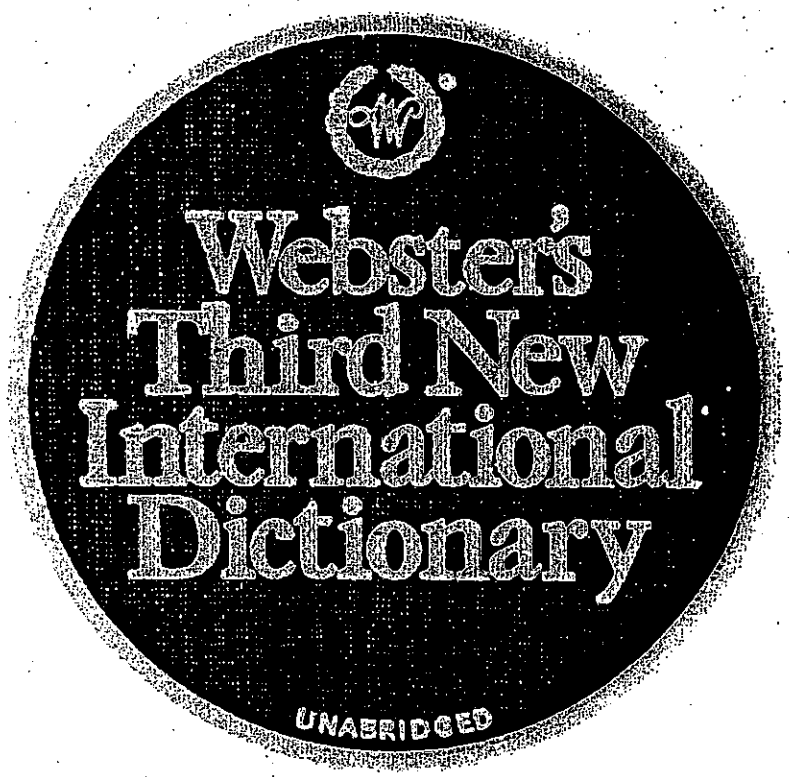
Lat. *incidēns*
on; see IN-[2].
in•ci•den•tal (ĭn′sĭ-dĕn′tl)
cur as an ur
minor, casua
— *n.* A mino
in•ci•den•tal•
dinate matter
-dĕnt′lē). Ap
incidental mu
dialogue of a
in•cin•er•ate
To cause to b
Lat. *incinerāt*
+ Lat. *cinis*,
in•cin•er•a•to
an apparatus,
in•cip•i•ent (ĭ
detecting inci
of *incipere*, t
cip′i•ence *n.*
in•ci•pit (ĭn′s
words of the
book. [Lat., t
INCEPTION.]
in•cise (ĭn-sīz′)
with a sharp
2.a. To engra
b. To engrave
ciser < OFr. *
incīs- : *in-*, in
in•cised (ĭn-sī
2. Made with
sharply cut: *th*
in•ci•sion (ĭn-si
cut into a boc
scar resulting
a leaf. **4.** The
in•ci•sive (ĭn-si
expression. —
in•ci•sor (ĭn-sī′
at the front of
in•cite (ĭn-sīt′)
urge on: *incith*
citer < Lat. *in*
IN-[2] + *citāre*,
kei-[2]*.] — **in•c**
in•ci•vil•i•ty (ĭ
dition of being
incl. *abbr.* **1.** In
in•clasp (ĭn-klăs
in•clem•ent (ĭn
2. Showing no
in•cli•na•ble (ĭ
cy or dispositic
in•cli•na•tion
the state of bei
the degree of de
b. An inclined
tain condition.
favor one thing
in•cline (ĭn-klīn′
deviate from th
posed to a cert
3. To lower or
— *tr.* **1.** To cau
have a certain t
or bow. — *n.* (
dient. [ME *enc*
into, toward; s
cli•ner *n.*

Syns: incl
meaning shared
enced toward a
clined to believe
admire him; pr
in•clined (ĭn-klī
2. Having a pre
inclined plane *n.*
to raise or lowe
in•cli•nom•e•te
to determine the
to the horizont
inclination of ar
3. See **clinomet**
in•close (ĭn-klōz′
in•clude (ĭn-klōōd
take in as a part
a secondary or
place into a gro
clūdere, to encl
— **in•clud′a•ble**

In·ci·dence (In′sĭ-dəns) *n.* **1.** The act or an instance of happening; occurrence. **2.** Extent or frequency of occurrence: *high incidence of malaria.* **3.** *Phys.* **a.** The arrival of radiation or a projectile at a surface. **b.** Angle of incidence.

EXHIBIT 18

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inched \'incht\ *adj* [*inch* + *-ed*] : having or measuring a specified number of inches ⟨a 4-*inched* hook⟩

inch·er \'inchə(r)\ *n* -s [*inch* + *-er*] : something having a dimension of a specified number of inches; *specif* : a gun having a bore of a specified number of inches — usu. used in combination with a numeral ⟨heard the 14-*inchers* firing on the coast⟩

in chief *adj* **1** : heading a staff : LEADING — often used in combination ⟨editor-*in-chief*⟩ **2** : PRIMARY, BASIC, INITIAL ⟨evidence *in chief*⟩ ⟨a fabric dutiable on its *in chief* value of wool⟩

inch·ling \'inchliŋ\ *n* -s [*inch* + *-ling*] : a small being of a kind likely to grow larger ⟨drew in a netful of ~s⟩

inch·ma·ree clause \'inchmə,rē-\ *n, usu cap I* [after *Inchmaree*, Brit. steamer; fr. its formulation as a result of the sinking of the Inchmaree in Liverpool harbor March, 1884] : a clause in a marine insurance policy on the hull of a ship that assuming the owners and managers of the ship have exercised due diligence makes the underwriter liable for loss or damage to hull or machinery arising from the negligence of the master, charterers, mariners, engineers or pilots from explosions, bursting of boilers, breakage of shafts, or any latent defect in hull and machinery, from contact with aircraft or land conveyances, or from any accident at docking facilities (as when loading or unloading or entering a dry dock)

inch·meal \'ᵊ,mē(ə)l\ *adv* [*inch* + *-meal* (as in *piecemeal*)] : little by little : GRADUALLY — often used with *by*

in·cho·ate \(')in,kōət, ən'kō-, 'inkə,wāt\ *adj* [L *inchoatus, incohatus*, past part. of *inchoare, incohare* to begin (lit., to hitch up), fr. *in-* ²in- + *cohum* strap fastening a plow beam to the yoke; perh. akin to Bret *morgo* hame, W *mynci* hame, OE *haga* hedge — more at HEDGE] : being recently begun or undertaken : INCIPIENT : being partly but not fully in existence or operation : INCOMPLETE; as **a** : imperfectly formed or formulated : DISORDERED, INCOHERENT, UNORGANIZED ⟨the general plan is ~ and incoherent, and the particular treatments disconnected —Hilary Corke⟩ ⟨the solar system . . . far out from the hub of this great wheel of stars and ~ dust and gas —L.C. Eiseley⟩ ⟨vague consumer longings and ~ needs —J.S.Gambs⟩ **b** *of a legal right or instrument or interest* : not yet perfected : not yet made certain or specific : not yet vested : INCIPIENT, EXPECTANT, POTENTIAL, CONTINGENT, IMPERFECTED ⟨an ~ right of dower⟩ ⟨an ~ equity⟩ ⟨an instrument that the law requires to be recorded is an ~ instrument until it is recorded —Besse May Miller⟩ — **in·cho·ate·ly** *adv* — **in·cho·ate·ness** *n* -es

²in·cho·ate \'inkə,wāt, ən'kō,āt\ *vb* -ED/-ING/-S [L *inchoatus, incohatus*, past part. of *inchoare, incohare*] *vi, archaic* : to cause to begin ~ *vt, archaic* : to make a beginning : START

in·cho·a·tion \,inkə'wāshən\ *n* -s [LL *inchation-, inchoatio, incohation-, incohatio*, fr. L *inchoatus, incohatus* + *-ion-, -io* -ion] : an act of beginning : COMMENCEMENT, INCEPTION

³in·cho·a·tive \(')in,kōəd·iv, ən'k-\ *n* -s [LL *inchoativum, incohativum*, fr. neut. of *inchoativus, incohativus*] : an inchoative verb

²inchoative \"\ *adj* [LL *inchoativus, incohativus*, fr. L *inchoatus, incohatus* + *-ivus* -ive] **1** : INITIAL, FORMATIVE ⟨~ stages⟩ **2** : denoting the beginning of an action, state, or occurrence — used of certain verbs (as *begin, set out, get, awake*) or of certain verb forms (as *tremesco* "I fall to trembling" and some other Latin verbs in *-sco*) — **in·cho·a·tive·ly** \-dv(l)ē\ *adv*

in·chon \(')in,chən\ *adj, usu cap* [fr. *Inchon*, Korea] : of or from the city of Inchon, Korea : of the kind or style prevalent in Inchon

inch-ounce *n* **1** : a unit of work equal to the work done in raising one ounce against the force of gravity through a distance of one inch **2** : a unit of moment equal to the moment of a force of one ounce acting at a distance of one inch from a center of moments

inch plant *n* : a wandering Jew (*Tradescantia fluminensis*) that is often grown as a house plant

inch-pound \'ᵊ,ᵊ\ *n* : one twelfth of a foot-pound

inch-ton \'ᵊ,ᵊ\ *n* : a unit of energy or work that is equal to the work done in raising one ton against the force of gravity the height of one inch

¹inchworm \'ᵊ,ᵊ\ *n* [*inch* + *worm*] : LOOPER 1

²inchworm \"\ *vb* : CRAWL

in·cide \ən'sīd\ *vb* -ED/-ING/-S [L *incidere* — more at INCISE] *vi* **1** *archaic* : CUT, INCISE **2** *obs* : to cause loosening or resolution ~ *vt* **1** *archaic* : to cut into (as a lesion or tissue) **2** *archaic* : to cause loosening or resolution of (as phlegm)

in·ci·dence \'in(t)səd·ən(t)s *also* -dᵊn- *or* -,den- \ *n* -s [ME, fr. MF, fr. LL *incidentia*, fr. L *incident-, incidens* + *-ia* -y] **1** *now chiefly dial* : INCIDENT **2 a** : an act or the fact or manner of falling upon or affecting : OCCURRENCE ⟨diseases of domestic ~ —*Science*⟩ ⟨control of both the ~ of expense and the meeting of expense must lie primarily in the hands of management⟩ **b** : rate, range, or amount of occurrence or influence ⟨a rising ~ of poverty⟩; *sometimes* : the rate of occurrence of new cases of a particular disease in a population being studied — compare PREVALENCE **3** : the falling of a tax upon a person who is unable to shift it onto someone else and who therefore bears the money burden of the tax ⟨the ultimate ~ of most corporation taxes is on the consumer⟩ — compare DIRECT TAX **4 a** : the arrival of something (as a projectile or a ray of light) at a surface **b** : ANGLE OF INCIDENCE 2

incidence wire *n* : STAGGER WIRE

incidency *obs var of* INCIDENCE

¹in·ci·dent \-nt\ *n* -s [ME, fr. MF, fr. ML *incident-, incidens*, fr. L, pres. part. of *incidere* to fall into, fall on, meet up with, occur, happen, fr. *in-* ²in- + *-cidere* (fr. *cadere* to fall) — more at CHANCE] **1 a** : an occurrence of an action or situation felt as a separate unit of experience : an occurrence or sometimes a situation or thing taking place as part of a larger continuum but unimportant or nonessential : HAPPENING ⟨conflict is an inevitable ~ in any active system of cooperation —Lewis Mumford⟩ **b** : an accompanying minor occurrence or condition : CONCOMITANT ⟨Madison's view . . . that taxation is a necessary ~ anyway to the exercise of any power —C.P.Curtis⟩ **c** : an occurrence noticeably varying a set or accustomed course or routine : an uncommon happening ⟨to remain at variance with his wife seemed to him a considerable ~ —Joseph Conrad⟩ **d** : an occurrence calling forth a sequel : a motivating event or situation : FACTOR ⟨the ~ of that conflict was slavery, but it was not its true cause —*Congressional Record*⟩ **e** : a happening or related group of happenings subordinate to a main narrative plot ⟨the melodrama and the romance . . . must be made up of swift successions of startling ~ —E.G.Sutcliffe⟩ **f** : a frequent, accustomed, or routine occurrence unworthy of note or comment ⟨a quiet ordinary ~ of daily life —Arnold Bennett⟩ **2 a** : a contretemps, fracas, disturbance, or other action likely to lead to grave consequences esp. in matters diplomatic ⟨repeated minor ~s led finally to the danger of open combat at the boundary —*Amer. Guide Series: Maine*⟩ **b** : a military situation marked by fighting without formally declared war ⟨the Korean ~⟩ **c** *chiefly Brit* : a bomb explosion or other sudden violent disturbance ⟨air-raid wardens checking on ~s⟩ **3 a** : something dependent upon, appertaining or subordinate to, or accompanying something else of greater or principal importance ⟨an alimony agreement may be an ~ of a divorce proceeding⟩ **b** : something arising or resulting from something else of greater or principal importance ⟨a power to employ a broker may be an ~ of an express power to sell real estate⟩ SYN see OCCURRENCE

²incident \"\ *adj* [ME, fr. L *incident-, incidens*, pres. part.] **1 a** : occurring or likely to occur esp. as a minor consequence or accompaniment ⟨confusion ~ to a quick change⟩ : associated or naturally related or attaching ⟨the privileges ~ to increased rank⟩ **b** *obs* : PERTINENT, APPOSITE, LIABLE, SUBJECT **2** *archaic* : occurring accidentally and without essential relationship : INCIDENTAL **3** *law* : dependent on or appertaining to another thing : directly and immediately relating to or involved in something else though not an essential part of it **4 a** : falling or striking on something — used esp. of light rays on a plane **b** : acting from without : EXTERNAL ⟨attacks in position or significance: as **a** : occurring merely by chance or without intention or calculation : occurring as a minor concomitant ⟨allowing a few dollars extra for ~ expenses⟩ ⟨the ~ gain which such a policy may win —J.A.Hobson⟩ ⟨man may be an ~ host of the sheep liver fluke⟩ **b** : being likely to ensue as a chance or minor consequence — usu. used with *to* ⟨labor problems ~ to rapidly expanding factories —*Amer. Guide Series: Mass.*⟩ **c** : lacking effect, force, or consequence : not receiving much consideration or calculation ⟨a cool, purely ~, and passive contempt —Herman Melville⟩ **d** : presented purposefully but as though without consideration or intention; *often* : DIGRESSIVE ⟨an ~ allusion, purposely thrown out, to the day of the week —Charles Dickens⟩ **2** : met or encountered casually or by accident : CHANCE ⟨~ traveling companions⟩ ⟨an ~ shipboard acquaintance⟩ SYN see ACCIDENTAL

²incidental \"\ *n* -s **1** : something that is incidental : a subordinate or incidental item ⟨no such ~ as personal sensibilities can be allowed to interfere with the overall plan of the survey⟩ **2** **incidentals** *pl* : minor items (as of expense) that are not particularized ⟨a bill for tuition and ~s⟩

in·ci·den·tal·ist \ˌᵊ,ᵊ'dent³list\ *n* -s : one that is more concerned with the minutiae of incident than with broad overall views or concepts

in·ci·den·tal·ly \ˌᵊ,ᵊdentlē, -t³lē, -li\ *adv* **1** : by chance : as a matter of minor import : CASUALLY ⟨in this discussion grave questions were ~ brought up⟩ **2** : by way of interjection or digression : in passing : PARENTHETICALLY ⟨touching ~ on the waterpower values⟩ ⟨another leading industry, ~, has quadrupled its business in five years⟩

incidental music *n* : descriptive music played or to be played during the action of a play to heighten a situation or project a mood (as of a battle, a storm, a death scene) or to relate directly to stage action (as a song or a dance); *broadly* : any music related to a play (as an overture or entr'acte) — compare BACKGROUND MUSIC

in·ci·den·tal·ness \ˌᵊ,ᵊ'dent³lnəs\ *n* -es : the quality or state of being incidental : CONCOMITANCE

in·ci·dent·less \'in(t)səd·əntləs, -dᵊn-, -,den-\ *adj* : free from incident : UNEVENTFUL

in·ci·dent·ly \'in(t)səd·əntlē, -dᵊn-, -li, ˌᵊ,ᵊdent- — *in sense 2 always the last*\ *adv* **1** : so as to be incident **2** : INCIDENTALLY

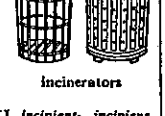
inciding *pres part of* INCIDE

in·ci·en·so \ˌin(t)sē'en(t)(ˌ)sō\ *n* -s [AmerSp, fr. Sp, incense, fr. L *incensum* — more at INCENSE] : a shrubby encelia (*Encelia farinosa*) of rocky desert uplands of the southwestern U. S. and adjacent Mexico that has grayish green to almost white tomentose foliage and showy cymes of yellow flowers and that produces a resin that has been used as incense, in folk medicine, and in varnish

in·cin·er·ate \ən'sinəˌrāt, *usu* -ād·+V\ *vb* -ED/-ING/-S [ML *incineratus*, past part. of *incinerare*, fr. L *in-* ²in- + *ciner-, cinis* ashes; akin to Gk *konis, konia* ashes, dust; basic meaning: to rub, scratch, tickle] *vt* : to cause to burn to ashes : consume by or as if by fire ⟨*incinerating* the trash⟩ ~ *vi* : to be or become completely burned ⟨paper and dry leaves ~ easily⟩

in·cin·er·a·tion \(ˌ)in,sinəˈrāshən, ənˌ-\ *n* -s [ML *incineration-, incineratio*, fr. L *incineratus* (past part. of *incinerare* to incinerate) + *-ion-, -io* -ion] : the act of incinerating or the state of being incinerated : CREMATION; *esp* : an analytical procedure for treating an organic substance with free access to air until only its ash remains — compare IGNITION

in·cin·er·a·tor \ə'insəˌrād·ə(r), -āiə-\ *n* -s : one that incinerates; *esp* : a furnace or a container for incinerating waste materials



Incinerators

¹in·cip·i·a·tive \ən'sipē,ād·iv, -ēəd-·\ *adj* [*incipient* + *-ative*] *of a verb form or aspect* : expressing action about to begin or just beginning — compare HABITUATIVE

²incipiative \"\ *n* -s : an incipiative form of a verb

in·cip·i·en·cy \ən'sipēənsē, -si\ *also* **in·cip·i·ence** \-ēən(t)s\ *n, pl* **incipiencies** *also* **incipiences** : the state or fact of being incipient : BEGINNING, COMMENCEMENT

in·cip·i·ent \(')in'sipēənt, ən's-\ *adj* [L *incipient-, incipiens*, pres. part. of *incipere* to begin, fr. *in-* ²in- + *-cipere* (fr. *capere* to take) — more at HEAVE] : beginning to be or become apparent : COMMENCING, INITIAL ⟨the ~ stage of a fever⟩ ⟨~ light of day⟩ ⟨~ civil disorders⟩ — **in·cip·i·ent·ly** *adv*

incipient species *n* : a natural population that is more or less interfertile with another related population but is inhibited from interbreeding in nature by some specific barrier — compare ECOSPECIES

incipient wilting *n* : partial and temporary loss of turgor in a plant that occurs in the presence of adequate soil moisture and is associated with excessive water loss through transpiration

in·ci·pit \'in(t)səpət, 'inkə-, *esp in senses b & c* 'incha-\ *n* -s [L, it begins, 3d pers. sing. pres. indic. of *incipere*] : BEGINNING: as **a** : the introductory words or part of a medieval manuscript or early printed book ⟨reproducing two ~s with superb miniatures —Raphael Levy⟩ — compare EXPLICIT **b** : the opening words of the text in a Gregorian chant or psalm tone sung by the cantor **c** : the word given at the beginning of the tenor in a cantus-firmus motet that serves as a reference to the tenor's origin in the liturgy

in·circumscription \ˌin+\ *n* [LL *incircumscription-, incircumscriptio*, fr. *incircumscriptus* not circumscribed (fr. L *in-* ²in- + *circumscriptus*, past part. of *circumscribere* to circumscribe) + L *-ion-, -io* -ion — more at CIRCUMSCRIBE] *archaic* : the quality or state of being free from bounds or limits

incircumspect *adj* [LL *incircumspectus*, fr. L *in-* ²in- + *circumspectus*, past part. of *circumspicere* to look around, be cautious — more at CIRCUMSPECT] *obs* : IMPRUDENT, INDISCREET

incircumspection *n, obs* — **incircumspectly** *adv, obs*

incisa *abbr* [L *incisus*] engraved

in·ci·sal \(')in'sīzəl\ *adj* [L *incisus* + E *-al*] : CUTTING ⟨the ~ edge of a tooth⟩

in·cise \(')in'sīz, -īs\ *vb* -ED/-ING/-S [MF or L; MF *incis-*, fr. L *incisus*, past part. of *incidere*, fr. *in-* ²in- + *-cidere* (fr. *caedere* to cut) — more at CONCISE] *vt, obs* : to make an incision in ~ *vi* **1** : to cut into : make an incision in ⟨*incised* the swollen tissue⟩ **2 a** : to carve figures, letters, or devices into : ENGRAVE ⟨~ a tablet with an inscription⟩ **b** : to produce (as letters, figures, or devices) by carving into a surface ⟨~ an inscription on a monument⟩ **3 a** : to produce (a narrow steep-walled valley) by downward erosion ⟨caused the streams to ~ their valleys —C.O.Dunbar⟩ **b** : to lower (itself) by eroding a deeper channel ⟨the streams then *incised* themselves to the new baselevel —C.O.Dunbar⟩ **c** : to intersect as a deep narrow cut ⟨more than twenty different submarine canyon systems ~ the continental border —J.C.Crowell⟩

incised *adj* **1 a** : CUT-IN, CARVED, ENGRAVED ⟨~ ornamentation⟩; *esp* : decorated with incised figures ⟨~ pottery⟩ **b** *of a cut or wound* : made with or as if with a sharp knife or scalpel : clean and well defined **2** : having a margin that is deeply and sharply and more or less irregularly notched ⟨an ~ leaf⟩

incised meander *n* : the curve of a winding river with steep slopes on both sides rising to a former floodplain and usu. interpreted as due to rejuvenation of a meandering stream but prob. also formed by a combination of vertical and lateral erosion in a single cycle of valley development — compare ENTRENCHED MEANDER

in·ci·si·form \ən'sizəˌfȯrm, -īsə-\ *adj* [*incisor* + *-iform*] : having the form of or resembling a typical incisor tooth : shaped for cutting

in·ci·sion \ən'sizhən\ *n* -s [ME *insicioun*, fr. MF & L; MF *incision*, fr. L *incision-, incisio*, fr. *incisus* + *-ion-, -io* -ion] **1 a** : a separation of parts made or such as might be made by a cutting or pointed instrument (as a notch in the margin of a leaf or of an insect's wing) **b** : CLEFT, CUT, GASH; *specif* : an incised wound made by a surgeon into the tissues or an organ

quality or state of being incisive (as in comprehension or action) : ACUTENESS, PENETRATION

in·ci·sive \(')in'sīsiv, ən'sī-, |ēv *also* |əv *sometimes* -īz\ *adj* [ML *incisivus*, fr. L *incisus* + *-ivus* -ive] **1** : having a cutting edge or piercing point : facilitating cutting or piercing ⟨as sharp and ~ as the stroke of a fang —T.B.Costain⟩ **2** : marked by sharpness and penetration esp. in keen clear unmistakable resolution of matter at issue or in pointed decisive effectiveness of presentation ⟨the clear, ~ genius which could state in a flash the exact point at issue —A.N.Whitehead⟩ ⟨the . . . irony . . . serves to put the literary crackpots in their proper place —S.C.Chew⟩ **3** : of, relating to, or situated near the incisors

SYN CLEAR-CUT, CRISP, TRENCHANT, CUTTING, BITING: INCISIVE indicates a keen penetration and sharp presentation that is effective or decisive ⟨Bismarck's will had not that *incisive*, rapier quality, that quality of highly tempered steel — flexible, unbreakable, of mortal effect, decisive, a sword — which had Richelieu's —Hilaire Belloc⟩ CLEAR-CUT indicates either unmistakably clear and lucid outlining, analysis, or presentation, or finite certainty defying disbelief or question ⟨this *clear-cut* and consistent political creed is set forth throughout with the lucidity and brevity that makes a first-class popular oration —*Times Lit. Supp.*⟩ ⟨the current decision . . . was neither *clear-cut* nor definite . . . it appeared to be an attempted compromise —*N.Y. Times*⟩ CRISP in this series has a variety of suggestions: keenness, freshness, clarity, animation, terseness, vigor, sureness, effectiveness ⟨a languorous work . . . with occasional interludes of *crisp* brilliance —Anthony West⟩ ⟨*crisp* epigrams —George Santayana⟩ TRENCHANT suggests sharp penetrating acuteness often in criticism or detraction and may suggest sarcastic asperity ⟨a *trenchant* critic of the rising capitalism, delighting in exposing the fallacies of the new economics and in pricking the bladders of political reputations —V.L.Parrington⟩ CUTTING and BITING apply to sharp sarcasm, ridicule, or detraction; the former may suggest a tendency to wound by penetrating acuteness, the latter a mordant, implacable harshness ⟨the *cutting* sarcasm . . . the cruel epigrams and occasional harsh witticisms —Jack London⟩ ⟨domineering and censorious of any that stood in his way, with a *biting* wit, although he mellowed somewhat as he grew older —T.D.Bacon⟩

incisive bone *n* : PREMAXILLA

incisive foramen *n* : a pit or in some animals two pits just behind the incisor teeth transmitting the nasopalatine nerves and the greater palatine artery

incisive fossa *n* : a depression on the front of the maxillary bone above the incisor teeth

in·ci·sive·ly \ə'vlē, -li\ *adv* : in an incisive manner: as **a** : CUTTINGLY ⟨outspokenly and ~ critical —W.A.Taylor⟩ **b** : with exactitude and precision ⟨high-court judges of long experience cannot ~ say how many laws are still in force —Mark Priestley⟩ ⟨enabled him to prove ~ that the concept of a Jewish race was erroneous —W.D.Wallis⟩

in·ci·sive·ness \ivnəs, |ēv- *also* |əv-\ *n* -es : the quality or state of being incisive; *esp* : concise precision of utterance or action

in·ci·sor \ən'sīzə(r), 'in,s- *sometimes* -īsə-\ *n* -s *often attrib* [NL, fr. LL, one that cuts, fr. L *incisus* + *-or*] : a tooth adapted for cutting; *esp* : one of the cutting teeth in mammals arising from the premaxillary bone of the upper jaw in front of the canines when canines are present or one of the corresponding teeth of the lower jaw — see DENTITION illustration

in·ci·sor·a \ˌin,sīˈhōrə, ˌin(t)səˈzh-\ *or* **in·ci·sure** \ən'sizhə(r)\ *n, pl* **incisu·rae** \-ə,rē\ *or* **incisures** [L *incisura*, fr. *incisus* + *-ura* -ure] : a notch, cleft, or fissure esp. of a body part or organ — **in·ci·sural** \ˌin,sīˈzhərəl, ˌin(t)səˈzh-; (ˌ)in'sīzhərəl\ *adj*

¹in·cit·ant \ən'sīt³nt\ *adj* [L *incitant-, incitans*, pres. part. of *incitare* to incite] : INCITING, CAUSATIVE, STIMULATING ⟨~ of infection⟩ ⟨an ~ factor⟩

²incitant \"\ *n* -s : an inciting agent; *esp* : a factor (as an infective agent) that is the essential causative agent of a particular disease ⟨where the fungal ~ is present mildew is likely to damage foliage in cold wet weather⟩

in·ci·ta·tion \ˌin,sī'tāshən, ˌin(t)sə'-\ *n* -s [MF, fr. L *incitation-, incitatio*, fr. *incitatus* (past part. of *incitare* to incite) + *-ion* -*io* -ion] **1** : an act of inciting : STIMULATION **2** : something that incites to action : INCITEMENT, INCENTIVE ⟨provocative statements that were an open ~ to violence⟩

in·cite \ən'sīt, *usu* -īd·+V\ *vt* -ED/-ING/-S [MF *inciter*, fr. L *incitare*, fr. *in-* ²in- + *citare* to put in movement, summon more at CITE] **1** : to move to a course of action : stir up : spur on : urge on ⟨*inciting* the people to rebel⟩ ⟨*incited* to further effects by his mother's enthusiasm⟩ **2** : to bring into being : induce to exist or occur ⟨such behavior is likely to ~ retaliation⟩ ⟨organisms that readily *incited* antibody formation⟩

SYN INSTIGATE, FOMENT, ABET: INCITE may indicate both an initiating, a calling into being or action, and also a degree of prompting, furthering, encouraging, or nurturing of activity ⟨his projects for *inciting* war between the two countries⟩ ⟨posters scattered by the thousands throughout the eastern states and Europe to *incite* immigration —*Amer. Guide Series: Minn.*⟩ ⟨their tutors had *incited* them to dig deeply in the older sources of learning⟩ ⟨did I see a young lady in want of a partner, gallantry would *incite* me to offer myself as her devoted knight —T.L.Peacock⟩ INSTIGATE implies initiating or encouraging others to initiate actions or feelings, often questionable actions initiated with dubious intention ⟨pogroms *instigated* or connived at by the government as a safety valve for popular discontent —W.R.Inge⟩ ⟨a comparative study, *instigated* by the director of the investigation, which classifies a series of nonliterate cultures⟩ FOMENT indicates persistent inciting, esp. of something thought of as seething or boiling ⟨radicals *fomenting* a rebellion⟩ ⟨race theories are indeed not only a modern invention to explain such group conflicts, but also a means for *fomenting* them —M.R.Cohen⟩ ABET is likely to indicate seconding, encouraging, or aiding some action already begun, esp. a questionable activity ⟨aiding and *abetting* a friend in obtaining money under false pretenses⟩ ⟨the general, *abetted* by the excited aide-de-camp, made a fatal error⟩ ⟨the will to achieve perfection, though not so rare as it sounds, is all too rarely *abetted* by leisure —Harry Levin⟩

in·cite·ment \-īt·mənt\ *n* -s **1** : the act of inciting or the state of being incited ⟨through emotional ~ of each other . . . they discover paths they need to know —Kathleen Spaull⟩ **2** : something that incites : INCENTIVE ⟨an ~ to further progress⟩

in·cit·er \-īd·ə(r), -īt·ə-\ *n* -s : one that incites

in·cit·ing·ly *adv* : so as to incite : in an inciting manner

in·ci·tive \(')in'sīd·iv, ən's-\ *adj* : tending to incite : expressive of incitement

in·ci·to·ry \-d·ərē\ *adj* : serving to excite : STIMULATORY

incity \(')in'sit, 'inˌsit\ *adj* [fr. the phrase *in city*] : lying wholly within or serving the area within a city ⟨~ and suburban bus lines⟩ ⟨the ~ edition of the paper⟩

in·civic \(')in+\ *adj* [*in-* + *civic*] : lacking civic responsibility

in·civil \"+\ *adj* [MF, fr. LL *incivilis*, fr. L *in-* ³in- + *civil* civil — more at CIVIL] : not civil : RUDE, BARBAROUS

in·civility \ˌin+\ *n* [MF *incivilité*, fr. LL *incivilitat-, incivilitas*, fr. *incivilis* + L *-itat-, -itas* -ity] **1** *obs* : INCIVILIZATION **2** : the quality or state of being uncivil : ill-bred behavior : DISCOURTESY, RUDENESS ⟨it is gross ~ to refuse to answer when spoken to⟩ ⟨never before met with such ~⟩ **3** : a rude or ill-bred act ⟨tired of his constant *incivilities*⟩

in·civilization \(ˌ)in+\ *n* [*in-* + *civilization*] : the state or being uncivilized

in·civism \(')in+\ *n* [F *incivisme*, fr. *in-* ³in- + *civisme* civism — more at CIVISM] : lack of civic-mindedness or of patriotism

incl *abbr* **1** inclosure **2** included; including; inclusive

inclasp *var of* ENCLASP

incld *abbr* included

incle *var of* INKLE

in-clearing \'ᵊ,ᵊ\ *n* [*¹in*] *Brit* : the checks received for payment by a bank during the process of clearing

in·clem·en·cy \(')in, ən+\ *n* [L *incl*ementia, fr. *inclemens*

in·ci·dence \'in(t)səd ən(t)s *also* -d°n- *or* -ˌden-\ *n* -s [ME, fr. MF, fr. LL *incidentia*, fr. L *incident-*, *incidens* + *-ia* -y] **1** *now chiefly dial* : INCIDENT **2 a** : an act or the fact or manner of falling upon or affecting : OCCURRENCE ⟨diseases of domestic ~ —*Science*⟩ ⟨control of both the ~ of expense and the meeting of expense must lie primarily in the hands of management⟩ **b** : rate, range, or amount of occurrence or influence ⟨a rising ~ of poverty⟩; *sometimes* : the rate of occurrence of new cases of a particular disease in a population being studied — compare PREVALENCE **3** : the falling of a tax upon a person who is unable to shift it onto someone else and who therefore bears the money burden of the tax ⟨the ultimate ~ of most corporation taxes is on the consumer⟩ — compare DIRECT TAX **4 a** : the arrival of something (as a projectile or a ray of light) at a surface **b** : ANGLE OF INCIDENCE 2

EXHIBIT 19

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 06-222 (JJF)

DECLARATION OF ERIC HOLLANDER, M.D.

I, Eric Hollander, M.D., declare as follows:

I have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. to testify on behalf of Plaintiff Wyeth in this litigation as an expert in the fields of psychiatry and psychopharmacology, including testimony relating to depression and anxiety, the treatment of depression and anxiety, antidepressants, anxiolytics, and the use and prescription of pharmaceuticals.

I. QUALIFICATIONS

My qualifications as an expert in these areas, as well as in other areas, are established by my *curriculum vitae*.

Briefly, I received a Bachelors of Arts in Psychology from Brandeis University in 1978, and a Medical Degree from State University of New York, Downstate Medical College, Brooklyn, New York in 1982. My residency training was in internal medicine and psychiatry at Mount Sinai Hospital in New York, New York from 1982-1986. I did a fellowship in psychopharmacology and anxiety disorders at Columbia University College

of Physicians and Surgeons and New York State Psychiatric Institute from 1986-1988. I have been practicing psychiatry continuously since 1986, and since 1993 at the Mount Sinai School of Medicine in New York. I have been teaching psychiatry at the Mount Sinai School of Medicine continuously since 1993.

Currently, I am the Esther and Joseph Klingenstein Professor and Chairman of Psychiatry at the Mount Sinai School of Medicine in New York. I am also Director of the Compulsive, Impulsive, and Anxiety Disorders Program, Director of Clinical Psychopharmacology, and Director of the Seaver and Greater New York Autism Center of Excellence at the Mount Sinai School of Medicine.

I am a Fellow of the American College of Neuropsychopharmacology and a Distinguished Fellow of the American Psychiatric Association. I have conducted extensive research in psychiatry, including depression and anxiety, have written more than 400 articles in psychiatry and psychopharmacology, and have extensively lectured at numerous international and national psychiatric professional conferences. I have received two national research awards from the American Psychiatric Association, a Distinguished Investigator Award from the National Alliance for Research in Schizophrenia and Depression and also received a Research Scientist Development Award from the National Institute of Mental Health ("NIMH"). I am also the Principal Investigator for the NIMH Institutional Research Training Grant for Training in Psychopharmacology and Outcomes Research. In addition, I edited or co-edited the texts Autism Spectrum Disorder (Marcel Dekker Inc. 2003), The American Psychiatric Textbook of Anxiety (American Psychiatric Press 2002), and Coping With Social Anxiety Disorder (Henry Holt & Co. 2005).

For further complete details regarding my qualifications and experience, including a list of the publications I have authored over the last ten years, a copy of my *curriculum vitae* is attached as Exhibit A.

II. PSYCHOPHARMACOLOGICAL MANAGEMENT OF MENTAL DISORDERS

Psychopharmacological management of both depressive and anxiety disorders involve selecting a proper medication based on both the efficacy and side effect profile of the medication. These medications often take several weeks to reach full effect and recommended treatment for most mood and anxiety disorders involves a course of treatment of at least 6-12 months. Early adverse side effects have a substantial impact on persistence or compliance with prescribed medications for these disorders. In fact, early adverse side effects are the number one reason for patients to discontinue medication early in the course of treatment. When patients discontinue, they are unable to obtain the benefit of the treatment and their recovery is compromised.

III. UNITED STATES PATENT NOS. 6,274,171B1, 6,403,120B1, AND 6,419,958B2

I have reviewed United States Patent Nos. 6,274,171 B1, 6,403,120 B1, and 6,419,958 B2 (the '171 patent, the '120 patent and the '958 patent respectively) and the correspondence between Wyeth and the United States Patent and Trademark Office that resulted in the patents' issuance, which I understand is called their prosecution histories.

The patents-in-suit indicate that immediate release venlafaxine hydrochloride ("venlafaxine IR") is associated with rapid dissolution, resulting in a rapid increase in blood plasma levels of the active compound shortly after administration, followed by a decrease in blood plasma levels over several hours until subtherapeutic plasma levels are approached after about 12 hours following administration. ['171 patent, col. 1, l. 66 to col. 2, l. 7]. As a result, multiple daily dosing is required. [*Id.*] The patents also note that the most common side effect with multiple daily dosed venlafaxine IR is nausea, experienced by about 45% of patients, and vomiting experienced in about 17% of patients. ['171 patent, col. 2, ll. 7-11].

The patents describe extended release formulations of venlafaxine hydrochloride which can be administered once a day. ['171 patent, col. 2, ll. 14-19]. Those

formulations provide a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period of time having specified peak blood plasma levels and diminished incidences of nausea and emesis as compared to the immediate release formulation. ['171 patent, col. 2, ll. 20-62].

The '171 patent's method claims recite a method for providing a therapeutic blood plasma concentration of venlafaxine over a 24 hour period with diminished incidences of nausea and emesis by giving orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours [claim 20], in about 5 to about 8 hours [claim 22], or in about six hours [claim 23], where venlafaxine hydrochloride is the active ingredient. Other method claims state a method for eliminating the peaks and troughs of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride by giving orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours [claim 21], in about 5 to about 8 hours [claim 24], or in about six hours [claim 25], where venlafaxine hydrochloride is the active ingredient.

The '958 patent claims 1-6 are almost identical to claims 20-25 in the '171 patent except that the word "encapsulated" is not present. Claim 1 of the '120 patent recites a method for providing a therapeutic blood plasma concentration of venlafaxine over a 24 hour period with diminished incidence of nausea and emesis by giving orally to a patient in need thereof, an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150 ng/ml, where venlafaxine hydrochloride is the active ingredient. [Claim 1]. Other claims require that the extended release formulation is encapsulated [claim 2] or provide that spheroids and encapsulated spheroids may be used in the invention [claims 13-14].

IV. The Meaning of the Patent Claim Term "Diminished Incidence[s] Of Nausea And Emesis"

I have considered the meaning of the claim term "diminished incidence[s] of nausea and emesis" in claims 20, 22 and 23 of the '171 patent, claims 1, 2, 13, and 14 of the '120 patent, and claims 1, 3 and 4 of the '958 patent.

Based upon my review of the '171, '958 and '120 patents and my education and experience, I understand the phrase "diminished incidence(s) of nausea and emesis" in the context of those patents to encompass the level, extent, degree, amount, range and/or frequency of nausea and vomiting. I understand that Impax's interpretation of "diminished incidence(s) of nausea and emesis" to be the number of patients suffering from nausea and vomiting. [Impax's April 13, 2007 claim construction].

Based upon my experience, limiting the word "incidence" to simply the number of patients, however, is not consistent with either my normal use of that word or the way that the '171, '958 and '120 patents use the word. While the term "incidence" certainly embraces the number of patients, I use and have used the word incidence in the past more broadly to include level, extent, degree, amount, range and/or frequency of the parameters measured. Although frequency is a different measure than severity or duration, I understand the term incidence as able to encompass all of these measures and that understanding is consistent with how the term "incidence" can be used in the fields of psychiatry or psychopharmacology. In my opinion, the level, extent, degree, amount and range of a side effect also can be encompassed within the term "incidence," and have an impact on whether or not the side effect is clinically meaningful.

Moreover, the '171, '958 and '120 patents describe the improvement in nausea and vomiting associated with the invention more broadly than simply a number of patients experiencing the adverse event. ['171 patent, col. 2, ll. 46-62]. I first note that

the claims of the patents require only "*diminished* incidence(s) of nausea and emesis[1]," rather than the cure or prevention of nausea and emesis. In my experience with many patients suffering from psychiatric disorders, partial relief of adverse events (such as nausea or vomiting) is quite significant and clinically meaningful and can mean the difference between adherence to treatment with the medicine and noncompliance. In fact, in my opinion, severity and duration of adverse events are the most important factors in achieving a successful long term outcome, such as remission, in the treatment of psychiatric disorders. When my patients have experienced nausea and emesis as a result of the administration of medication, vomiting usually is immediately preceded by severe nausea. Thus, if a patient's vomiting can be reduced or eliminated, the degree or duration of nausea experienced, even if not eliminated, often is less severe.

The abstract of the patents state that the extended release dosage form "further provides a lower incidence of nausea and vomiting than the conventional tablets." [Abstract, ll. 1-7]. The specification of the patents further discuss improvements provided by the invention as follows:

> The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine

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1 I understand from my review of the patents' specification that the nausea and emesis are diminished as compared to the immediate release formulation of venlafaxine hydrochloride. See, for example, Abstract ll. 1-7. Specifically, I understand the patents' use of the term "diminished" in the patents' claims to mean that the nausea and emesis resulting from the once-a-day administration of the claimed extended release formulation to be less that what would be experienced by patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day.

> hydrochloride tablets in two eight-week and one 12 week clinical studies.

['171 patent at col. 2, ll. 46-55]. The patents then describe a method for using the extended release formulations in the treatment of patients, such that

> in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

['171 patent at col. 2, ll. 55-62].

Consistent with my normal use of the words, I understand the patents to be using the words "level" and "incidence" interchangeably based upon the Abstract's description of the improvement in side effects achieved by the invention as "a lower incidence of nausea and vomiting," and the specification's discussion of a reduction in "the level of nausea and incidence of emesis."

In addition, the specification describes improvements in nausea and emesis not as limited to only the complete absence of nausea or emesis during the course of treatment, but as including a reduction in those side effects after initial administration. Such an improvement is consistent with Wyeth's construction of "diminished incidences of nausea and emesis" (a reduction in the "degree and/or frequency of nausea and emesis"), which would include such an improvement. It is not consistent with Impax's construction ("a decrease in the number of patients suffering from nausea and vomiting"), however, because that construction would treat patients identically regardless of the severity of nausea or vomiting, including whether or not a patient who suffers from nausea and vomiting upon initial treatment then adapts to the medication and thereafter suffers less frequent or less severe nausea and vomiting.

The patents also are consistent with my observation that treatment with extended release Effexor® XR results in less nausea and vomiting than treatment with immediate release Effexor®. In my personal experience prescribing Effexor®, side effects were a rate limiting step in the overall acceptance of this drug in the treatment of depression, anxiety, etc. This is probably why Effexor® got the widespread nickname of "SideEffexor." In particular, nausea and vomiting were clinically significant early side effects which substantially interfered with patient compliance and, therefore, limited the utility of this treatment to those patients with severe depression who failed to respond to other treatments., *i.e.*, often inpatients with melancholic depression.

In contrast, when Effexor® XR was launched[2] I noticed shortly thereafter that this formulation had less nausea and vomiting in the course of treatment, and that this difference was clinically meaningful. Fewer patients experience nausea with Effexor® XR than with Effexor®. For those patients who do experience nausea with Effexor® XR, it is less intense and less severe, has a shorter duration, and there is less accompanying vomiting as compared to patients taking Effexor®. For those patients who do experience vomiting, the frequency and severity of vomiting is less for Effexor® XR as compared to Effexor®. This is consistent with my discussions with colleagues who also reported better tolerability and adherence to treatment with Effexor® XR as compared to Effexor®, resulting in greater likelihood of remission.

Given the better tolerability of Effexor® XR as compared to Effexor®, I can now use it with a much broader and more diverse group of patients, including outpatients

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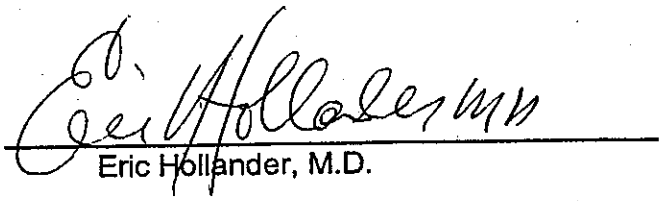
[2] Since its launch, I have treated well over one hundred patients with Effexor® XR, most of whom had both depressive and anxiety symptomatology. A number of these patients were initially treated with Effexor®, but were not able to tolerate that treatment, often specifically because of early nausea and vomiting. For many of these patients, Effexor® XR was well tolerated and patients were able to remain on treatment to the point that they had a remission of the underlying disorder.

with depression, patients with mild to moderate depression, patients with various anxiety disorders including GAD and SAD, and other conditions. In my opinion, it was the extended release formulation of Effexor® XR that unlocked the full potential of the drug venlafaxine.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 7th day of May 2007 at New York, New York.



Eric Hollander, M.D.

EXHIBIT A

CURRICULUM VITAE

ERIC HOLLANDER, MD, DFAPA, FACNP

Present Positions: Esther and Joseph Klingenstein Professor and Chair
Director-NIH STAART Greater New York Autism Center of Excellence
Director-Seaver Autism Research Center
Director-Compulsive, Impulsive and Anxiety Disorders Program
Director-Clinical Psychopharmacology
Department of Psychiatry
Mount Sinai School of Medicine
One Gustave L. Levy Place, Box 1230
New York, N.Y. 10029

Telephone Number: 212/659-8287
FAX Number: 212/987-4031
E-Mail: eric.hollander@mssm.edu

Born: Los Angeles, California (6/19/57)

Education:

1978	B.A.	Brandeis University, Waltham, MA
1982	M.D.	State University of New York Downstate Medical College, Brooklyn, NY

Internship:

1982 - 1983	Internal Medicine	Mount Sinai Hospital, NY, NY

Residency:

1983 - 1986	Psychiatry	Mount Sinai Hospital, NY, NY
1985 - 1986	Chief Resident-Psychiatry Research	Clinical Research Unit and Alzheimer's Disease Research Center - Mount Sinai School of Medicine, NY, NY

Fellowship:

1986 - 1988	NIMH Psychiatry Research Fellowship	Columbia University College of Physicians & Surgeons and NYS Psychiatric Institute
1988 - 1989	Dana Foundation Fellow	Columbia University
1988 - 1993	NIMH Research Scientist Development Award	Columbia University

Licensure:

New York State License: 155389 Year: 1983

DEA License: AH2289420

Diplomate - American Board of Psychiatry and Neurology (29504) 1987

Honors:

2005, Best Doctors, NY Magazine

2005, Chair - NIH STAART Autism Steering Committee

2005, Secretary/Treasurer - International Society for Research In Impulsivity (ISRI)

2005, Director – International College of Obsessive Compulsive Spectrum Disorders (ICOCS)

2005, Chair – DSM-V Research Planning Agenda Workgroup on Obsessive Compulsive Behavior Spectrum Disorders

2005, Member – APA Practice Guidelines – Obsessive Compulsive Disorder

2003, Distinguished Fellow – American Psychiatric Association

2003, Substance Abuse and Mental Health Administration (SAMHSA) National Registry of Effective Prevention Programs (NREPP), U.S. Department Of Health and Human Services

2003, Best Doctors, *New York Magazine*

2002, Fellow – American College of Neuropsychopharmacology

2002 – present, Chair - DSM-V Work Group on Obsessive Compulsive Spectrum Disorders, APA

2002, Best Doctors In America

2002, Autism Clinical Trials Task Force, Cure Autism Now (CAN)

2002, Best Doctors, *New York Magazine*

2001, Best Doctors, *New York Magazine*

2001, Best Doctors, *New York Post*

2000-2001, Society of Biological Psychiatry, George N. Thompson Award Committee

1999, Fellow, American Psychiatric Association

1998, NARSAD Distinguished Investigator Award

1998, Full Membership, American College of Neuropsychopharmacology

1999, Section Editor, ACNP, Neuropsychopharmacology: The Fifth Generation of Progress

1998, DSM-IV-R Work Group Chair, Impulse Control Disorder Section

1998, Nolan D.C. Lewis Visiting Professor and Scholar, Carrier Foundation

1997, Scientific Director, CNS Research Foundation

1996, Founding Editor
CNS Spectrums: The International Journal of Neuropsychiatric Medicine

1996, Scientific Advisory Board, Anxiety Disorders Association of America

1994, Best Mental Health Specialists in the U.S.A. - Good Housekeeping

1994, The Best Doctors in America, Woodward/White, Inc.

1993, Chairman, OC Foundation Awards Committee

1993, International OCD Council Founding Member

1993, Secretary, OCD Section, World Psychiatric Association

1992, Member, DSM-IV Work Group - Obsessive Compulsive Disorder

1992, Member, DSM-IV Work Group - Body Dysmorphic Disorder

1992, Scientific Advisory Board, OC Foundation

1991, American College of Neuropsychopharmacology, Associate Member

1990, American Psychiatric Association/Wisnieski Young Psychiatrist Research Award, First Place, New York, NY

1990, Collegium Internationale Neuro-Psychopharmacologium Rafaelsen Fellowship Award, Kyoto, Japan

1988-1993, Research Scientist Development Award
National Institute of Mental Health

1988-1989, Dana Foundation Fellow (Columbia University)

1986, American Psychiatric Association/Penwalt Resident Research Award, First Place, Washington, DC

1986, Marcel Heiman Memorial Award for Outstanding Research
Mount Sinai School of Medicine, Department of Psychiatry

1986, M. Ralph Kaufman Prize, Outstanding Resident in Psychiatry
Mount Sinai School of Medicine, Department of Psychiatry

1985-1986, Solomon W. Ginsburg Fellow: Group for the Advancement of Psychiatry

1978, General Honors, Brandeis University

Patents and Inventions:
Oxytocin in Autism and Social Attachment Disorders (US patent issued)
Mementine in Autism, Compulsive and Impulsive Disorders (US patent application)
Fluoxetine in Autism (Orphan Designation: Food and Drug Administration)
Internet Addiction - YBOCS (US Copyright)

Pathological Gambling – YBOCS (US Copyright)
Fluvoxamine Gambling Treatment Program (SAMHSA)

Founding Editor: *CNS Spectrums: The International Journal of Neuropsychiatric Medicine*

Editorial Advisory Board: *Neuropsychopharmacology (1997 – 1999)*

Research In Autism Spectrum Disorders

World Journal of Biological Psychiatry

Medscape Psychiatry & Mental Health

Psychiatric Annals

Focus on OCD

Primary Psychiatry (past)

Mental Fitness

International Journal of Psychiatry in Clinical Practice

Journal of Gambling Studies

Wager

Clinical Neuropsychiatry

Contemporary Psychiatry

Mount Sinai Journal of Medicine (Associate Editor)

Reviewer: *Archives of General Psychiatry*

American Journal of Psychiatry

Biological Psychiatry

Psychiatry Direct

Psychiatry Research

Journal of Neuropsychiatry and Clinical Neuroscience

Journal of the American Medical Association

Journal of Nervous and Mental Disorders

Hospital Appointments:

1986 - 1992 Assistant Attending Psychiatrist, The Presbyterian Hospital

1992 - 1993 Associate Attending Psychiatrist, The Presbyterian Hospital

1988 - 1993	Attending Psychiatrist, The New York State Psychiatric Institute
1988 - 1993	Director, Obsessive Compulsive Disorder Biological Studies Program The New York State Psychiatric Institute
1989 - 1993	Director, Anxiety Diagnostic & Recruitment Unit, NYS Psychiatric Institute
1993 - 1994	Associate Director, Academic Affairs, Queens Hospital Center
1993 - 1994	Vice Chairman, Department of Psychiatry, Mount Sinai School of Medicine
1993 - Present	Director, Clinical Psychopharmacology, Mount Sinai School of Medicine
1994 - 2003	Clinical Director, Seaver Autism Research Center
1994 - Present	Director, Compulsive, Impulsive and Anxiety Disorders Program
1996 - Present	Attending Psychiatrist, The Mount Sinai Hospital
2003 – Present	Director, Seaver Autism Research Center
2003 – Present	Director, Greater NY Autism Research Center of Excellence

Academic Appointments:

1986 - 1988	Instructor in Clinical Psychiatry, Columbia University P & S
1988 - 1992	Assistant Professor of Clinical Psychiatry, Columbia University P & S
1992 - 1993	Associate Professor of Clinical Psychiatry, Columbia University P & S
1993 - 1996	Associate Professor of Psychiatry, Mount Sinai School of Medicine
1996 - Present	Professor of Psychiatry, Mount Sinai School of Medicine

Teaching (Mount Sinai School of Medicine and Columbia University P & S):

Phenomenology Course – PGY II Residents

Neuroscience Course – PGY III Residents

Outpatient Psychopharmacology Course - PGY III Residents

Psychopharmacology Supervision - PGY III Residents

Anxiety Disorder Lectures - MS I and MS II Medical Students

OCD Lectures - PGY II and III Psychiatry and Neurology Residents

Neuroscience Review Course - Neurology Department

Outpatient Psychopharmacology Clinic - PGY III Residents

OCD CME Course Director - 8 Conferences at Mt. Sinai and Columbia

Journal Club and Grand Rounds - chair, Mt. Sinai/Queens Hospital Center

Pharmacology Lectures - MS IV Medical Students

Chairman and Organizer, 7 Conferences on the Diagnosis, Neurobiology, Genetics and Treatment of Autism in association with CAN, NAAR, ASA, and NARSAD

Chairman and Organizer
- First International Conference on OCD, Capri, March 1993
- Second International Conference on OCD, Guadaloupe, March 1996
- Third International Conference on OCD, Madeira, Portugal, 1998
- Fourth International Conference on OCD, St. Thomas, V.I., 2000
- Fifth International Conference on OCD, Sardinia, 2001
- Sixth International Conference on OCD, Lanzarote, 2003

Participant, Anxiety Disorders in African-Americans Conference, 1993

Fellowship Supervisor, Program for Minority Research Training in Psychiatry
American Psychiatric Association

Professional Organizations:

Academia, Medicina & Psychiatria Foundation (Fellow)

American College of Neuropsychopharmacology
- Fellow (2002)
- Member (1998-Present)
- Finance Committee (1999-present)
- Section Editor, ACNP, Psychopharmacology: The Fifth Generation of Progress
- Editorial Advisory Board, Neuropsychopharmacology
- Associate Member (1992-1996)

American Federation for Clinical Research

American Medical Association

American Psychiatric Association (Distinguished Fellow)
Member, Committee on Resident Research Award Review

American Psychopathological Association

American Society of Clinical Psychopharmacology

Anxiety Disorders Association of America (Scientific Advisory Board)

Asociacion Argentina de Trastornos de Ansiedad

Collegium Internationale Neuro-Psychopharmacologicum

European College of Neuropsychopharmacology - Corresponding Member

Group for the Advancement of Psychiatry
Solomon Ginsburg Fellow (1985-1986), Medical Education Committee

International College of Obsessive Compulsive Spectrum Disorders (Company Director)

International Council on OCD (Founding Member)

International Society for Research on Impulsivity and Impulse Control Disorders
President Elect - 2006
(Secretary Treasurer - FY2005)

National Board of Medical Examiners (Test Material Development Committee)

Obsessive Compulsive Foundation (Scientific Advisory Board)

Society of Biological Psychiatry
Scientific Program Committee
George N. Thompson Award Committee

World General Medical Council (Fellow)

World Health Organization Committee on Priority Treatments for Mental Health Disorders
Priority Treatments for Obsessive Compulsive Disorder

Consulting:

US Congress and Senate, Joint Committee on NIH Funding Issues

Psychopharmacology Consult, Health and Hospitals Corporation

Scientific Advisory Boards
Obsessive Compulsive Foundation
Anxiety Disorders Association of America
CNSR Foundation
Autism Society of America Foundation
QSAC
NAMI
Cure Autism Now

Scientific Advisory Boards
Solvay Pharmaceuticals
Abbott Neuroscience
Wyeth-Ayerst Laboratories
SmithKline Beecham
Lilly Neuroscience
Ortho-McNeil
Roche Laboratories
Pfizer Pharmaceuticals
Pharmacia/Upjohn
Callisto Pharmaceuticals, Inc.
Somaxan Pharmaceuticals

Medical Lecture Program/Speakers Program
Abbott Pharmaceuticals
Bristol Myers/Squibb Pharmaceuticals
Eli Lilly and Company
Forrest Pharmaceuticals
GlaxoSmithKline
Novartis Pharmaceuticals

Pfizer Pharmaceuticals
Pharmacia/Upjohn
Smith Kline Beecham
Solvay Pharmaceuticals
Wyeth Ayerst Laboratories

First International OCD Conference Organizer - Solvay/Upjohn - 1993, Capri
Second International OCD Conference Organizer - Solvay/Upjohn - 1996, Guadaloupe
Third International OCD Conference Organizer - Solvay/Upjohn - 1998, Madeira
Fourth International OCD Conference Organizer – Solvay/Upjohn – 2000, St. Thomas
Fifth International OCD Conference Organizer – Solvay/Upjohn – 2001, Sardinia
First, Second, Third Columbia University OCD Conference Organizer - Ciba Geigy/CME
First Mt. Sinai/OC Foundation OCD Conference - 1994 - Solvay/Upjohn
First, Second, Third Mt. Sinai/Seaver Center Autism Conference
First Mt. Sinai/Seaver Center Autism Conference for Educators

Administrative:

Director, Anxiety Diagnostic and Recruitment Unit
MHCRC, New York State Psychiatric Institute

Director, Compulsive and Impulsive Disorders Program
New York State Psychiatric Institute

Director, Open Treatment Component
Mental Health Clinical Research Center
New York State Psychiatric Institute

Member, Quality Assurance Committee
New York State Psychiatric Institute
Queens Hospital Center

Member, Incident Review Committee
New York State Psychiatric Institute

Member, Medical Staff Committee
New York State Psychiatric Institute
Queens Hospital Center

Member, Continuing Medical Education Committee
Columbia University, College of Physicians and Surgeons

Member, Medical Education Committee, Medical Ethics
Group for the Advancement of Psychiatry

Member, Scientific Program Committee
Society for Biological Psychiatry

Consultant, Health and Hospitals Corporation
Psychopharmacology Issues

Member, Managed Care Committee - Psychiatry
Mount Sinai School of Medicine

Member, Operating Committee
Mount Sinai School of Medicine

Member, Continuing Medical Education Committee, Postgraduate School
Mount Sinai School of Medicine

Member, Promotions Committee
Mount Sinai School of Medicine

Chair, Outpatient Psychiatry Research Committee
Mount Sinai School of Medicine

Chair, Psychiatry Research Incident Review Board
Mount Sinai School of Medicine

Chair, Space Appropriations Committee, Psychiatry Outpatient Research Center, Atran E
Mt Sinai School of Medicine

Patient Advocacy Groups

Obsessive-Compulsive Foundation
Member, Scientific Advisory Board
Director, Scientific Awards Committee
Member, Minorities and Research Committee

International Obsessive-Compulsive Council
Founding Member
Secretary

Anxiety Disorders Association of America
Member, Scientific Advisory Board

World Psychiatric Association, Section on Anxiety and OCD
Secretary

Cure Autism Now,
Chair, Scientific Advisory Group – Treatment Guidelines
Chair, Autism Clinical Trials Task Force (ACTTF)
Chair – Clinical Trials Network (CTN)

Committees
Incident Review Committee - NYS Psychiatric Institute
Faculty Staff Committee - NYS Psychiatric Institute
Quality Assurance Committee - NYS Psychiatric Institute, Queens Hospital Center
Chairman - Grand Rounds Committee - Queens Hospital Center
Chairman - Journal Club Committee - Queens Hospital Center
Operating Committee - MSSM Psychiatry Department
Senior Investigators Committee - MSSM Psychiatry Department
Clinical Directors Committee - MSSM Psychiatry Department
Affiliate Clinical Directors Committee - MSSM Psychiatry Department
Trauma Committee - Victim Services, Inc.
Trauma Planning Subcommittee - Victim Services, Inc.
Service Directors Committee - Queens Hospital Center
Managed Care Committee - Mt. Sinai School of Medicine
Continuing Medical Education Committee – Mt. Sinai School of Medicine
Promotions Committee – Mt. Sinai School of Medicine

Grant Reviewer
NIMH – 1996-2005 - RO1, K grants, RUPP-PI
NIDA – 1995-2003 - RO1, K grants

Current Funded Grants:
Principal Investigator

(2003-2008). NIH – Greater New York Autism Research Center of Excellence: The STAART Program. (1 U54 MH66673-01). Annual Direct Cost $ 1,417,295 Total Direct Cost $ 7,149,157.

(2003-2008). NIH – Greater New York Autism Research Center of Excellence: The STAART Program. (1 U54 MH66673-01). Liquid Citalopram Supplement. Annual Direct Cost $ 100,000.

(2003-2008). NIMH - NRSA Institutional Research Training Grants – Training in Psychopharmacology and Outcomes Research (1 T32 MH62996-01). Annual Annual Direct Cost $ 50,127 Total Costs $ 455,353.

(2005-2008). FDA – Fluoxetine in Pediatric Body Dysmorphic Disorder (FD-R-002613-01) Annual Direct Cost $ 289,387 Total Direct Cost $ 884,873.

(2001-2006). FDA – Fluoxetine vs. Placebo In Adult Autistic Disorder. (FD-R-002026-01) Annual Direct Cost $ 203,771 Total Direct Cost $ 607,930.

(2001-2006). NINDS – Divalproex Sodium/Placebo In Child/Adolescent Autism. (1 R21 NS43979-01) Annual Direct Cost $ 100,000 Total Direct Cost $ 300,000.

(1994-2006). Seaver Foundation - Seaver Autism Research Center (Eric Hollander, M.D., Director) Annual Cost $ 1,250,000 Total Cost $ 13,000,000.

(2006-2007). CAN – Clinical Trials Network Infrastructure. Annual Direct Cost $ 102,488 Total Direct Cost $ 112,737.

(2006-2007). CAN – A multi-site double-blind placebo-controlled trial of memantine vs. placebo in children with autism targeting motor skills. Annual Direct Cost $ 54,393 Total Direct Cost $ 59,842.

Co-Principal Investigator

(2000-2004). CDC – Pharmacotherapy of Sexually Compulsive MSM – Jonathan Morgenstern, PI, Annual Direct Cost $ 244,172 Total Direct Cost $ 712,324.

(1998-2003). Solvay Pharmaceuticals - Brain Imaging of the Effects of Lithobid and Lithium Carbonate In Bipolar and Cyclothymic Patients - Monte Buchsbaum, PI, Total Direct Cost $ 252,000.

Co-Investigator

(2000-2006). NIDA – Interdisciplinary Training In Drug Abuse Research (T32 DA 07135-21) – Stuart C. Sealfon, M.D., P.I., Annual Direct Cost $ 359,568 Total Direct Cost $ 1,797,840.

Pending Grants:
Principal Investigator

NIMH – Lithium vs. Naltrexone vs. Placebo in Impulse Dyscontrol (Pathological Gambling)
Annual Direct Cost $ 225,000 Total Direct Cost $ 381,375

NIMH – Risperidone vs. Quetiapine vs. Placebo in Resistant OCD
Annual Direct Cost $ 225,000 Total Direct Cost $ 381,375

Prior Funded Grants

(1998-2003). FDA - Liquid Fluoxetine vs. Placebo in Child/Adolescent Autism. (FD-R-001404-01) Annual Direct Cost $ 116,242 Total Direct Cost $ 349,637 Total Cost $ 592,635.

(1999-2003). NIMH - Pharmacotherapy of Adolescent Body Dysmorphic Disorder (1 RO1 MH58935-01A1) Annual Direct Cost $ 66,578 Total Direct Cost $ 112,850 Total Cost $ 475,247.

(2002-2003). Abbott Laboratories – An Open-Label Trial of Divalproex Sodium Extended Release In Borderline Personality Disorder. Total Direct Cost $ 143,115.00.

(2001-2003). Pfizer Pharmaceuticals – Efficacy of Sertraline in the Treatment of Binge Eating Disorder Among Obese Children and Adolescents. Total Direct Cost $ 50,000.

(2001-2003). Forrest Laboratories – Treatment of Internet Addiction with Citalopram. Total Direct Cost $ 50,000.

(2001-2003). Contral Pharma – Nalmefene in the Treatment of Pathological Gambling: A Placebo Controlled Dose Reponse Study. Total Direct Cost $ 100,000.

(2001-2003). Pfizer – Multicenter Trial of Ziprasidone Augmentation in Serotonin Reuptake Inhibitor-Resistant Obsessive-Compulsive Disorder. Total Direct Cost $ 144,663.

(2001-2003). Callisto – Autoimmune Investigations In Obsessive-Compulsive Disorders. Total Direct Cost $ 10,000.

(2001-2003). Pfizer – Phase II, Twelve Week, Double Blind and Placebo Controlled Study To Evaluate the Safety and Efficacy of Two Doses of CP-448,187 (1.5mg and 3.0mg) In Subjects with Obsessive Compulsive Disorder. Total Direct Cost $ 100,000.

(1998-2003). Abbott Laboratories – Divalproex Sodium vs. Placebo In Childhood/Adolescent Autism: A Double-Blind Placebo Controlled Study Followed by Fluoxetine Augmentation. Total Cost $ 86,000.

(1998-2003). Lilly Laboratories – Olanzapine vs. Placebo Crossover Study of Autistic Disorder: Effect of fMRI Imaging. Total Cost $ 150,000.

(1998-2003). Bristol-Myers Squibb - Serzone Treatment Study in Pathological Gambling. Total Direct Cost $ 40,000.

(1998-2003). Solvay Pharmaceuticals - Double-Blind Parallel Trial of Lithobid, Lithium Carbonate and Placebo In Lithium Treatment Naive Bipolar and Cyclothymic Patients Presenting To A Pathological Gambling Clinic. Total Annual Direct Cost $ 127,306 Total Cost $ 254,612.

(1998-2003). PBO Foundation - Research and Clinical Program for OCD and Related Disorders. Total Annual Direct Cost $ 90,910.

(1997-2003). Janssen Pharmaceuticals - Risperidone in Refractory OCD: Positron Emission Tomography Imaging. Annual Direct Cost $ 120,000.

(1995-2003). Lilly Research Labs - Prozac and Regional Metabolic Activity in Autism. Total Direct Cost $ 30,000.

(1998-2003). Smith-Kline Beecham – A Double-Blind Placebo-Controlled Flexible Dose Study of the Efficacy and Tolerability of Paroxetine on Generalized Anxiety Disorder. Total Direct Cost $ 60,120.

(1999-2003). Solvay Pharmaceuticals – A Multicenter, Double-Blind, Randomized, Parallel Group Study of the Efficacy and Safety of a Flexible Dose Regimen of Fluvoxamine CR versus Placebo in Outpatients with Obsessive Compulsive Disorder. Total Direct Cost $ 100,000.

(1999-2003). Abbott Pharmaceuticals – Divalproex Sodium vs Placebo in Intermittent Explosive Disorder. Total Direct Cost $ 100,000.

(1999-2003). Solvay Pharmaceuticals – Fluvoxamine vs. Placebo In the Treatment of Generalized Social Phobia. Total Direct Cost $ 100,000.

(1998-2002). NIMH - Divalproex Sodium/Placebo In Borderline PD (1 RO3 MH56974-01). Annual Direct Cost $ 49,988 Total Direct Cost $ 99,762 Total Cost $ 169,097.

(1997-2002). NIDA - Serotonergic/Norepinephrine Function in Pathological Gambling. (1 RO1 DA10234-01A2) Annual Direct Cost $ 251,126 Total Direct Cost $ 984,926 Total Cost $ 1,669,450.

(1997-2001). Glaxo-Wellcome - Sumatriptan Challenge In Autism and Asperger's Disorder. Total Direct Cost $ 50,000.

(1998-2000). Cure Autism Now - Fluoxetine/Placebo Treatment of Childhood/Adolescent Autism: Clinical Predictors & Dimensional Severity. Total Cost $ 56,100.

(1998-1999). Cure Autism Now - D8/17 Positivity in Autism: Implications for Etiology, Subtyping and Treatment. Total Cost $ 15,000.

(1998-1999). NARSAD Distinguished Investigator Award - D8/17 Positivity in Autism: Implications for Etiology, Subtyping and Treatment. Total Cost $ 85,525.

(1988-1993). NIMH Research Scientist Development Award - "Psychobiology of Obsessive Compulsive and Related Disorders", NIMH. MH-00750. Annual Costs $ 72,150, Total Costs $ 360,750.

(1994-1997). FDA Orphan Drug Grant - Clomipramine/Desipramine Crossover in BDD (FD-R-000941-01) Annual Direct Costs - $ 198,871 Total Direct Cost $ 398,600

(1995-1998). Abbott Pharmaceuticals - Valproate Treatment of Borderline Personality Disorder. Total Direct Cost $ 25,000.

(1997-1998). SmithKline Beecham Pharmaceuticals - A Double-Blind, Placebo-Controlled, Flexible Dosing Trial to Evaluate the Efficacy of Modified Release Paroxetine In the Treatment of Panic Disorder. Annual Direct Cost $ 25,000.

(1997-1998). Upjohn Pharmaceuticals - Double Blind Placebo Controlled Fluvoxamine

Treatment of Pathological Gambling. Annual Direct Cost $ 100,000.

(1994-1996) Upjohn Pharmaceuticals - Double Blind Placebo Controlled Fluvoxamine Treatment of Pathological Gambling. Annual Direct Cost $ 100,000.

(1993-1994). Solvay Pharmaceuticals - Fluvoxamine/Clomipramine Treatment of OCD. Annual Direct Cost $ 52,500.

(1992-1993). Smith Kline Pharmaceuticals - Effect of Paroxetine on SPECT/Cerebral Blood Flow in OCD. Annual Direct Cost $ 15,000.

(1989-1994). Mental Health Clinical Research Center (NIMH) - Open Treatment Component (DF Klein, PI) $ 200,420.

(1990-1992). American Psychiatric Association/McArthur Foundation - DSM-IV Field Trial for Obsessive-Compulsive Disorder. Annual Direct Cost $ 10,000.

(1991-1993). Smith Kline Beecham Pharmaceuticals - Paroxetine Treatment of Obsessive-Compulsive Disorder. Annual Direct Cost $ 100,000.

(1990-1991). Child Psychiatry Research Center Grant - Psychobiology of Childhood Obsessive-Compulsive Disorder. $ 2,220.

(1990-1991). Child Psychiatry Research Center Grant - Follow-up Study: Collaborative Perinatal Project Soft Signs and Anxiety Disorders. $ 2,000.

(1990-1991). Biomedical Research Support Grant - Research Foundation for Mental Hygiene to New York State Psychiatric Institute. Psychobiology of Impulsive Personality Disorders. $ 3,000.

(1988-1989). Biomedical Research Support Grant - Research Foundation for Mental Hygiene to New York State Psychiatric Institute. 5HT Enhanced Cerebral Blood Flow and Auditory Evoked Potentials and Repeat Challenges During Treatment in OCD. $ 6,200.

(1988-1989). Biomedical Research Support Grant - Columbia University College of Physicians and Surgeons. Apomorphine Challenges in Cocaine Abuse. $ 5,000.

(1987-1988). Biomedical Research Support Grant - Research Foundation for Mental Hygiene to New York State Psychiatric Institute. Biological Challenges in Normal Controls. $ 4,500.

(1987). Biomedical Research Support Grant - Research Foundation for Mental Hygiene to New York State Psychiatric Institute. Biological Challenges in Obsessive-Compulsive Disorder. $ 3,642.

(1987). Biomedical Research Support Grant - Research Foundation for Mental Hygiene to New York State Psychiatric Institute. Neuropsychiatric Investigations of Obsessive-Compulsive Disorder. $ 4,964.

B. Co-Principal Investigator

NIMH - MH43845-Psychobiology of Obsessive Compulsive Disorder. 35% Effort. (Dr. M. Liebowitz, PI), Total Direct Costs $ 356,412.

NIMH - MH44175-A Family Study of Obsessive Compulsive Disorder. 10% Effort.

(Dr. Abby Fyer, PI). Total Direct Costs $ 464,798.

(1991). Biomedical Research Support Grant - Research Foundation for Mental Hygiene - Neuropharmacology and Neuropsychology of Pathological Gambling. (C. DeCaria, PI). $ 4,490.

(1991). Biomedical Research Support Grant - Research Foundation for Mental Hygiene - CT Findings and Soft-Signs in OCD (D. Stein, PI). $ 2,000.

C. Director

Mental Health Clinical Research Center (NIMH). Anxiety Diagnostic and Recruitment Center Component (DF Klein, PI). $ 508,000.

D. Co-Investigator

NIMH-Endogenous ERP's in Obsessive Compulsive Disorder. RO1 Grant. (J. Towey, PI) Total Direct Costs $ 133,461.

NIMH-Chlorimipramine and Behavior Therapy for Obsessive Compulsive Disorder. RO1 Grant. (M. Liebowitz, PI) Total Direct Costs $ 766,224.

(1988-1989). Biomedical Research Support Grant - Research Foundation for Mental Hygiene to New York State Psychiatric Institute. M-CPP Challenge in Eating Disorders (C. Buttinger, PI) $ 5,000.

E. Overall Preceptor

NAAR/Bristol-Myers Squibb Research Fellowship in Autism and Neuropharmacology
Neuropharmacology, Neuroimaging, Immunology, Molecular Biology, and Molecular Genetics
Charles Cartwright, M.D. Total Annual Direct Cost $ 60,000

NAAR/Bristol-Myers Squibb Research Fellowship in Autism and Neuropharmacology
Neuropharmacology, Neuroimaging, Molecular Neurobiology
Sherie Novotny, M.D. Total Annual Direct Cost $ 60,000

Prior Co-Investigator

(1996-2000). NIMH First Award - Fluoxetine vs. Placebo Treatment of Depersonalization Disorder (MH55582) - Daphne Simeon, PI, Annual Direct Cost $ 70,000.

(1996-1998). Theodore & Vada Stanley Foundation - Positron Emission Tomography and Emotion Interpretation in Autistic Adults - Bonnie Aronowitz, PI, Annual Direct Cost $ 64,000.

Selected Presentations:

Over 300 scientific presentations at American Psychiatric Association, Society of Biological Psychiatry, American College of Neuropsychopharmacology, World Federation of Societies of Biological Psychiatry, Psychiatry Research Society, International Catecholamine Conf, Neuropharmacology of Serotonin Conf, AEP, CINP, ECNP and at many grant rounds at psychiatry departments in the USA and Europe/South America/Africa.

Chairman-Scientific Symposium

1988 Society of Biological Psychiatry - "Obsessive Compulsive Disorders"
1989 American Psychiatric Association - "Predictors of Treatment Outcome in OCD"
1989 American Psychiatric Association - "Overlap of Tourette's Syndrome & OCD"
1989 World Federation Societies Biological Psychiatry
"Update on Drug Treatment of OCD" and "Psychobiology of OCD"
1990 American Psychiatric Association - "Update on the Treatment of OCD"
1990 American Psychiatric Association - "Overlap of Eating Disorders and OCD"
1991 Columbia University CME - "New Directions in OCD"
1992 American Psychiatric Association - "Obsessive-Compulsive Related Disorders"
1992 American Psychiatric Association - "Impulsivity and Compulsivity"
1993 First International OCD Conference, Capri
1993 American Psychiatric Association - "OCD Spectrum Disorders"
1994 American Psychiatric Association - "OCD Spectrum" and "Neuropsychology of OCD"
1994 CINP, Washington, DC - "New Developments: Functional Imaging of OCD and TS"
1995 American Psychiatric Association -
"Overview and Psychopharmacology of Body Dysmorphic Disorder"
"Impulsivity and Compulsivity: Phenomenology and Treatment"
1996 American College of Neuropsychopharmacology -
"Oxytocin in Neuropsychiatric Illness: Studies Relevant to Autism";
"Strategies for Defining a More Homogeneous Phenotype of Autism for Family/ Genetic Studies"
1996 American Psychiatric Association - "OCD: State of the Art and Practical Management"
1997 American Psychiatric Association -
"Gambling: Biological/Genetic, Treatment, Government and Gaming Concerns"
"Predictors of Treatment Response in Mood and OCD-Related Disorders"
"Recent Advances in Autism and Asperger's Disorder"
"CNS Spectrums - Emerging Neuropsychiatric Concepts"
1998 American Psychiatric Association –
"Genetics of OCD"
1998 American College of Neuropsychopharmacology
"Neuropsychopharmacology of Pathological Gambling"
1999 American Psychiatric Association –
"New Perspectives in the Treatment of Impulsivity"
2000-2005
Multiple symposia at APA, ACNP, NCDEU annual meetings

Fellows:

1. Dan J. Stein, M.D.
Columbia University/NYS Psychiatric Institute Postdoctoral Research Fellow
NARSAD Young Investigator Award - "Psychobiology of the Personality Dimensions"

2. Daphne Simeon, M.D.
Columbia University/NYS Psychiatric Institute Postdoctoral Research Fellow
NIMH Postdoctoral Research Fellowship
NARSAD Young Investigator Award - "Depersonalization: Diagnosis, Biology, Treatment"

3. Michael Hwang, M.D.
Program for Minority Research Training in Psychiatry, American Psychiatric Association
"Neurological Aspects of OCD and TS"

4. Allison McCarley
Program for Minority Research Training in Psychiatry, American Psychiatric Association
"Sexual Side Effects of Serotonin Reuptake Blockers:
Stanley Scholar Program, Columbia University

5. Robert Grossman, M.D.
NIMH Postdoctoral Research Fellow - Mt. Sinai School of Medicine
Psychobiology of Self-Injurious Behavior

6. Scott Cherkasky, M.D.
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Dissertation Committee:

1. Concetta DeCaria - Doctor of Philosophy in Psychology (Neuropsychology)
Dissertation: "Psychobiology of Pathological Gambling"

Current Research Activities:
Neuropharmacology/
Neuropsychiatry/
Functional Imaging/
Pharmacological and Psychological Treatment/
of
Autism
Obsessive-Compulsive Disorder
Body Dysmorphic Disorder
Pathological Gambling
Impulsive/Aggressive Personality Disorders
Impulse Control Disorders
OC Related Disorders

Publications

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EXHIBIT 20

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 06-222 (JJF)

DECLARATION OF RONALD J. SAWCHUK, Ph.D.

I. QUALIFICATIONS

I, Ronald J. Sawchuk, Ph.D., declare as follows:

I have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. to testify on behalf of Plaintiff Wyeth in this litigation as an expert in the field of pharmacokinetics.

I am a Professor of Pharmaceutics at the University of Minnesota, a position I have held since 1983. I have studied and carried out research in the field of pharmacokinetics for over thirty years.

I received my Ph.D. in 1972 from the University of California, San Francisco in pharmaceutical chemistry with a focus on pharmacokinetics. Immediately upon receiving my degree, I became an Assistant Professor of Pharmaceutics at the University of Minnesota and was promoted to Associate Professor in 1977. I have been a Professor of Pharmaceutics since 1983 and

was Acting Head of the Pharmaceutics Department from 1983 to 1986, and Head from 1998 to 1999. I have served as Director of Graduate Studies for the Pharmaceutics Program for nine years. I have advised on the order of thirty graduate students, postdoctoral fellows, and visiting scholars on projects relating to preclinical and clinical pharmacokinetics and bioanalytical chemistry.

A major focus of my research at the University of Minnesota has been in neuropharmaceutics and in the delivery of drugs to the central nervous system. One goal of this work was to enhance the distribution of centrally acting agents to the brain. This research included the targeting of antiviral compounds to brain tissue in an effort to optimize the delivery of drugs used in treating HIV encephalopathy. An area of emphasis here was the use of transport inhibitors to alter the distribution of such agents across the blood-brain barrier. Similar studies have been undertaken in my laboratory to examine factors that affect access of other centrally acting drugs to the brain. As an extension of this research, I am currently working with a medical device company on the delivery of a centrally acting drug into cerebrospinal fluid in animal and human subjects. Current work in my laboratory addresses the absorption and distribution of antibiotics to sites of infection.

I have taught, and continue to teach, pharmacokinetics, neuropharmacokinetics, and pharmacokinetic modeling and simulation in professional, graduate, and elective courses at the University of Minnesota and/or in the pharmaceutical industry for the past thirty years. I have

expertise in the determination of pharmacokinetic parameters for rapid and slow release formulations, the assessment of oral absorption using deconvolution, bioanalytical chemistry, and biopharmaceutics.

I have devoted a large part of my career to the study of the pharmacokinetics of several classes of drugs, exhibiting linear and nonlinear disposition. In addition to authoring numerous publications in this area, I have received funding from various sources in the public and private sector to support my research in pharmacokinetics, including support from the National Institutes of Health ("NIH") and the U.S. Food and Drug Administration ("FDA"). I have also consulted with the pharmaceutical industry in projects involving pharmacokinetics and biopharmaceutics, including bioequivalence, bioavailability, and bioanalytical chemistry.

I am a member of many scientific and professional societies, and have been elected as a Fellow of both the American Association of Pharmaceutical Scientists ("AAPS") and the American Association for the Advancement of Science ("AAAS"). In addition, I am a member of the Executive Council of the AAPS, and serve on the Editorial Board of the Journal of Pharmaceutical Sciences.

In addition to my academic qualifications, I am the owner of Biopharmakon, through which I act as an independent consultant to the pharmaceutical industry with respect to pharmacokinetics, bioanalytical chemistry, and biopharmaceutics.

For further details regarding my experience and qualifications, including the publications I have authored over at least the past ten years, a copy of my curriculum vitae is attached (Exhibit A).

1. Pharmacokinetics

Pharmacokinetics is the study of the absorption, metabolism, distribution, and excretion of drugs in animals or humans. Each of these processes can affect the ultimate disposition of the drug. For example, in order to reach the intended site of action, a drug administered orally usually must first be absorbed from the gastrointestinal tract into the bloodstream. If the drug cannot be absorbed, then it simply passes through the gastrointestinal tract and is eliminated from the body without having the chance to exert its therapeutic effect at the intended site. Many drugs are metabolized, or converted into other chemicals during the absorption process, e.g., in the intestinal tract or in the liver. This conversion may result in the loss of a substantial amount of active ingredient. On the other hand, the metabolism of some drugs results in their conversion into other pharmacologically active compounds.

Once in the bloodstream, drugs may then be distributed to different tissues of the body. Although the liver is considered to be the major site of metabolism for most drugs, blood-borne enzymes and several other organs, such as the kidney, the lung, and the brain, may also metabolize certain drugs. Finally, orally administered drugs are eliminated entirely from the body via

various processes. The pharmacokinetics of a particular drug thus depends on a complicated interplay of processes that occur within the body.

In essence, pharmacokinetics can be considered as the study of how the body acts upon the drug. One of the goals of pharmacokineticists is to determine the rate and extent of drug exposure that a patient will experience following oral dosing. Pharmacokinetics also offers a means to compare the rate and extent of drug exposure provided by different formulations of the same drug.

In a clinical setting, pharmacokineticists often determine the concentration of the drug in a subject's plasma over time in order to understand how the body processes the drug after it has been ingested. They typically graph the drug plasma concentration as a function of time. The peak plasma concentration of drug achieved after oral dosing of a subject with drug is typically called Cmax, and the time it takes to reach the peak plasma concentration is referred to as Tmax. The Cmax and Tmax are often used to assess the performance of alternative dosage forms.

2. Biopharmaceutics

Biopharmaceutics is a study of the relationship between the physicochemical properties of a drug or its dosage form and the biological effects they produce. This would include, *e.g.*, dissolution characteristics of a drug and/or dosage form. The dissolution characteristics of a dosage form can be of critical importance when developing an oral extended release formulation. The goal of an extended release formulation is to retard the release of the active

drug from the dosage form, thus resulting in a slower rate of absorption than one would expect from an immediate release formulation. Dissolution testing aids in the development of dosage forms for *in vivo* testing. If release of drug from a dosage form can be slowed down in *in vitro* testing, then it can be tested *in vivo* to determine whether or not it can be absorbed into the blood in sufficient quantities to maintain therapeutic levels. The slower absorption rate may be reflected in the drug plasma concentration versus time curve (discussed above), and may have significant pharmacological consequences. Researchers often correlate the *in vitro* dissolution profile with the actual absorption of the drug from the dosage form when it is tested *in vivo*. Once *in vivo* trials are performed, this type of information can be used, *inter alia*, to help develop additional dosage forms of the drug that would be expected to exhibit similar *in vivo* characteristics.

B. United States Patent Nos. 6,274,171, 6,403,120 and 6,419,958

I have reviewed United States Patent Nos. 6,274,171 ("the '171 patent"), 6,403,120 ("the '120 patent") and 6,419,958 ("the '958 patent"). The three patents[1] contain claims to methods for providing therapeutic blood plasma levels of venlafaxine over a twenty-four hour period using extended release

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1 I understand that the three patents share essentially the same specification. I will therefore cite only to the '171 patent unless specifically noted otherwise. The citations will be in the form of "column number:line number." These citations are understood to reflect the corresponding passages in the specifications of U.S. Ser Nos. 60/014,006; 08/821,137, 08/964,328, 09/884,412, 09/488,629 and 09/950,965, which also support the meaning of the claim terms discussed herein.

formulations. These patents recite certain distinct pharmacokinetic characteristics of venlafaxine extended release formulations, such as the time period it takes to achieve peak concentrations of drug in plasma (for example, claim 20 of the '171 patent and claim 1 of the '958 patent), or the maximum concentration of drug achieved in plasma after oral administration (for example, claim 1 of the '120 patent). The patents describe one aspect of the invention as "an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug [ ] component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period." [Col. 2:14-18]. The patents further note that the claimed formulation results in a "flattened drug plasma concentration to [sic] time profile," which eliminates the multiple sharp peaks and troughs associated with multiple daily dosing of the immediate release formulation. [Col. 2:20-28].

The patents also make clear that nausea and vomiting were common side effects produced by the immediate release dosage form of venlafaxine hydrochloride:

> With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

[Col. 2:7-11]. The patents further state that the use of the extended release dosage forms results in an improved nausea and vomiting profile relative to the treatment with the conventional formulation. [Col. 2:55-62].

The patents include additional information pertaining to the claimed extended release dosage forms of venlafaxine hydrochloride. For example, Table 1 of the patents describes the dissolution profile of the extended release dosage form of the invention, and the associated text further states that "[c]onformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form." [Col. 6:42-45]. In my opinion, the patents thus teach that the dissolution profile reported in Table 1 is correlated to the desired pharmacokinetic parameters described in the claims at issue. I would expect venlafaxine hydrochloride dosage forms that exhibit this dissolution profile to exhibit the claimed *in vivo* characteristics.

Tables 2 and 3 provide concentration-time data resulting from multiple dose and single dose studies utilizing both an extended release venlafaxine hydrochloride formulation of the invention as well as an immediate release venlafaxine hydrochloride formulation. These data are consistent with the conclusion that the drug in the extended release product is both released and absorbed more slowly than from the immediate release product.

Thus, the patents-in-suit teach formulations that would be reasonably expected to behave *in vivo* in the manner claimed: a formulation having the *in vitro* dissolution profile described in Table 1 would be, according to the patents in suit, reasonably expected to display the *in vivo* characteristics depicted in Tables 2 and 3. Conformance with this profile is expected to provide the

requisite *in vivo* therapeutic blood plasma levels over a twenty-four hour period. [*See, e.g.*, col. 6:42-45].

C. The Meaning of "A Method For Eliminating the Troughs and Peaks of Drug Concentration in a Patients Blood Plasma Attending the Therapeutic Metabolism of Plural Daily Doses of Venlafaxine Hydrochloride"

I have considered the meaning of the phrase "a method for eliminating the troughs and peaks of drug concentration in a patient(')s blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride" in claims 21, 24 and 25 of the '171 patent and claims 2, 5 and 6 of the '958 patent. This phrase refers to a method in which the extended release formulation is given to a patient over the course of treatment once daily, which results in a rise in venlafaxine blood plasma concentration, followed by a generally protracted decrease over the rest of the 24 hour period, which eliminates the multiple peaks and troughs in venlafaxine plasma concentration when the same daily dose of the immediate release dosage form of venlafaxine hydrochloride is administered to a patient two or three times daily. The phrase also means that the blood levels experienced by a patient treated with an extended release formulation of venlafaxine hydrochloride during a 24 hour period are therapeutic—that is, sufficient to provide relief from the condition being treated over the course of therapy.

This meaning is consistent with my understanding of the plain meaning of the terms in this phrase and the patent specification. In my view, pharmacokineticists would understand that a once-a-day oral extended release dosage form of venlafaxine hydrochloride would, by design, provide a slower

rate of release *in vivo* than what was observed with the immediate release dosage form, resulting in a decrease in dosing frequency, and an altered plasma concentration-time profile.

Thus, the patents, which describe the use of venlafaxine hydrochloride as an important drug for the treatment of depression (col. 1:59-61), describe the plasma concentration-time profile of the immediate release formulation as follows:

> Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug.

[Col. 1:63-col. 2:7]. Thus, the conventional, immediate release form of venlafaxine hydrochloride requires multiple daily dosing to avoid subtherapeutic drug plasma levels. This would result in multiple sharp peaks and troughs in plasma concentration over the course of a single day of treatment in order to maintain therapeutic plasma levels for the full 24 hour period.

In contrast, the patents describe one aspect of the invention as "an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug [ ] component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period." [Col. 2:14-18].

The patents further note that the claimed formulation results in a "flattened drug plasma concentration to [sic] time profile," which eliminates the multiple sharp peaks and troughs associated with multiple daily dosing of the immediate release formulation. [Col. 2:20-28]. The drug plasma concentration versus time curve is further characterized as follows:

> In essence, the plasma levels of venlafaxine [ ] hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four [sic, hour] period.

[Col. 2:28-36]. This passage is consistent with how one of skill in the art would understand the claim phrase "A method for eliminating the troughs and peaks ... " in the context of the specification as a whole. For example, because of rapid release and absorption of the drug from the conventional immediate release formulation, the absorption process ends sooner resulting in "peak blood plasma levels in 2 to 4 hours." [Col. 2:36-38]. This rapid absorption causes plasma levels to decrease rapidly such that "subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug." [Col. 2:4-7]. The specification also states that "this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets." [Col. 2:20-45 at 24-28]. Because the extended release formulation of

venlafaxine hydrochloride is administered only once a day, only one peak and one trough in venlafaxine plasma concentration are observed over a twenty-four hour interval. This clearly differs from the plasma concentration-time profile of the immediate release product, dosed two or three times daily, which would result in two or three peak-trough pairs in the twenty-four hour period, since each dosing interval during the day would exhibit its own peak and trough plasma concentration of drug.

Moreover, the sharp peaks and troughs associated with the immediate release formulation are replaced with a single peak and a flatter concentration-time profile that rises and falls more slowly. Accordingly, the patent specification notes that the claimed extended release formulation "provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day. . . ." [Abstract, lines 1-7; see also, col. 1:63-2:7].

Thus, my understanding of this claim phrase is consistent with the definition proposed in Wyeth's April 13, 2007 construction: A method in which the extended release formulation is administered once in a 24-hour period, resulting in a venlafaxine blood plasma concentration that rises to a maximum value, followed by a generally protracted decrease over the remaining period while maintaining during that 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated, thereby eliminating the multiple sharp peaks and

troughs resulting from multiple daily dosing of the same total daily dose of the immediate release formulation as reflected in a graph of venlafaxine blood plasma concentration versus time.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 7th day of May 2007, at Washington, D.C.

Ronald J. Sawchuk, Ph.D.

EXHIBIT A

RONALD J. SAWCHUK

PERSONAL DATA

Present Address:	Department of Pharmaceutics College of Pharmacy Room 9-143 Weaver-Densford Hall University of Minnesota 308 Harvard Street S.E. Minneapolis, MN 55455 Telephone: (612) 624-0646 FAX: (612) 624-0951 E-mail: sawch001@umn.edu
Home Address:	14934 Pixie point Circle SE Prior Lake, MN 55372 Telephone: (952) 226-6507
Born:	May 29, 1940, Toronto, Ontario, Canada
Marital Status:	Married, three children
Citizenship:	Dual: U.S. and Canadian

EDUCATION

1959	(High School)	Oakwood Collegiate Institute, Toronto Secondary School Grade XIII)
1963	B.Sc. Phm.	University of Toronto, Toronto Ontario College of Pharmacy Licentiate No. 10748
1966	M. Sc. Phm.	University of Toronto, Toronto
1972	Ph.D.	University of California, San Francisco Pharmaceutical Chemistry (Pharmacokinetics)

PROFESSIONAL AND ACADEMIC EXPERIENCE

1963 - 1965	Teaching Assistant, University of Toronto
1966	Community Pharmacist (part-time), Toronto
1966 - 1968	Teaching Assistant, University of California
1971 - 1972	Instructor in Pharmaceutics, University of Minnesota
1972 - 1977	Assistant Professor of Pharmaceutics, University of Minnesota
1977 -1983	Associate Professor of Pharmaceutics, University of Minnesota
1974 - 1982	Associate Director, Clinical Pharmacokinetics Laboratory, U of Minnesota
1982 - 1995	Director, Clinical Pharmacokinetics Laboratory, College of Pharmacy, U of Minnesota
1983 - present	Professor of Pharmaceutics, University of Minnesota
1983 - 1989	Director of Graduate Studies in Pharmaceutics, University of Minnesota
1983 - 1986	Acting Head, Department of Pharmaceutics, University of Minnesota
1984 (summer)	Quarter Leave, Sandoz Pharma, Pharmacokinetics and Drug Metabolism Dept., Basel, Switzerland (M. Lemaire)
1991 - 1994	Director of Graduate Studies in Pharmaceutics, University of Minnesota
1992 (Summer)	Quarter Leave, Sandoz Pharma, Drug Safety, Basel, Switzerland (W. Niederberger)
1996 - 1999	Member, Board of Directors, Century Mortar Club
1997 (Spring)	Semi-Quarter Leave, Toyama Medical and Pharmaceutical University, Japan (H. Sato)
1997 (Summer)	Semi-Quarter Leave, Novartis AG, PKDM, Basel, Switzerland (J. Vonderscher)
1998 - 1999	Head, Department of Pharmaceutics, University of Minnesota
2001 (Summer)	Faculty Development Leave, Novartis AG, PKDM, Basel, Switzerland (M. Lemaire)

CURRENT PROFESSIONAL RESPONSIBILITIES

1972 - present	Member, Graduate Program in Pharmacutics, University of Minnesota
1983 - present	Professor of Pharmaceutics, University of Minnesota
1982 - present	Consultant to the pharmaceutical industry
1995 - present	Director, Bioanalytic and Pharmacokinetic Services, University of Minnesota
1995 - present	Editorial Board, *Saudi Pharmaceutical Journal*
1996 - present	Editorial Board, *Journal of Pharmaceutical Sciences*
1996 - present	Member, Graduate Program in Neurosciences, University of Minnesota
2001 - present	Member, Graduate Program in Experimental and Clinical Pharmacology, U of M
2002 - present	Member, Graduate Program in Social, Administrative and Clinical Pharmacy, U of M

OTHER PROFESSIONAL ACTIVITIES AND RESPONSIBILITIES

Prepared two videotapes on "Pharmacokinetics" for undergraduate instruction
Co-editor of a book with James Blanchard, Ph.D. and B.B. Brodie, Ph.D., entitled "Principles and Perspectives in Drug Bioavailability." S. Karger, Publisher, 1979
Assistant Director, Clinical Pharmacokinetics Laboratory, 1974-82
Consultant in the Establishment and Implementation of the Drug Quality Assurance Program, United Hospitals, St. Luke's Division, St. Paul, 1975
Participant in Critical Incidents Workshop, PDI - College of Pharmacy, 1977
Assessor in the Pharmacy Assessment Exercises, 1978
Coordinator for Continuing Education in Pharmacy, TV Series 1978, 1980
Expert, Bureau of Drugs and Biologics, Food and Drug Administration, 1982-84
Screening Committee, Abstracts, Basic Pharmaceutics Section, APS, APhA, 1981
Review of Grants, Medical Research Council (Canada) 1980-86
Review of Grants, British Columbia Health Care Foundation, 1981-84
Advisory Consultant, Site Visit Team NIH (NINCDS) Yale University School of Medicine, October 1979
Member, Site Visit Team NIH (NINCDS) University of Utah School of Medicine, January 1983
Member, Special Pharmacology Study Section NIH, April-June 1988
Review of Grants, Idaho State Board of Education, 1989-91
Review of Grants, Greater Minnesota Corporation, 1990-91
Organizer and Symposium Co-Chair, "Microdialysis in Drug Metabolism and Disposition Studies", for the Annual AAPS Meeting, San Antonio TX, 1992
Symposium Co-Chair, "Kinetic and Dynamic Challenges of the 90's", for the Annual AAPS Meeting, San Diego, CA, 1994
Organizing Committee Member for the NATO Advanced Study Institute, "Pharmacokinetics: From Theory to Practice", Erice, Italy, April 5-16, 1994
Co-organizer and Participating Instructor, "Pharmacokinetics for the Pharmacist and Pharmaceutical Scientist" University of Milan, Varese, September 10 -15, 1995.
Member, Board of Directors, Century Mortar Club, 1996-present.
National Advisory Committee, FAMU RCMI Program, Tallahasse, FL 1996-present
Co-organizer and Participating Instructor, "Pharmacokinetics for the Biomedical and Pharmaceutical Scientist" University of Milan, Varese, September 7 -12, 1997.
Scientific Advisory Committee, 1st Symposium on Microdialysis and Pharmacokinetics, Leiden, The Netherlands April 1998
Organizer and Participating Instructor, "Pharmacokinetics for the Biomedical and Pharmaceutical Scientist" University of Malta, Msida, September 6 -15, 1998.
Founder, Microdialysis Focus Group, American Association of Pharmaceutical Scientists, 1998.
Scientific Advisory Committee, 2nd International Symposium on Microdialysis in Drug Research and Development, Stockholm, Sweden, June 2000
Chair, Microdialysis Focus Group, American Association of Pharmaceutical Scientists, 1998-2000.
Co-Chair, Organizing Committee, 3rd International Symposium on Microdialysis in Drug Research and Development, Minneapolis, MN, USA, June 2002
Visiting Professor, Guilin Medical College, Guilin PRC (2002-2007)

Scientific Advisory Committee, 4th International Symposium on Microdialysis in Drug Research and Development, Vienna, Austria, June 2004
Scientific Advisory Committee, Abbott Laboratories, for the FDA Critical Path Initiative, September 2004
Scientific Advisory Committee, 5th International Symposium on Microdialysis in Drug Research and Development, Leiden, The Netherlands, June 2006

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

American Association of Pharmaceutical Scientists (Fellow)
American Association for the Advancement of Sciences (Fellow)
American Pharmacists Association (APhA)
American Society for Pharmacology and Experimental Therapeutics
International Society of Anti-Infective Pharmacology
International Society for the Study of Xenobiotics
Century Mortar Club (Board of Directors, 1996-98)
Rho Chi

SCHOLARSHIPS, HONORS AND AWARDS

1964	Scholarship, Canadian Foundation for the Advancement of Pharmacy
1965-66	National Research Council of Canada
1965	Warner-Lambert Research Fellowship
1968-70	National Institute of Health (NIH) Training Grant
1981-82	Teacher of the Year, College of Pharmacy, University of Minnesota
1986	Recipient of Horace T. Morse-Amoco Foundation Award
1988	Fellow, American Association of Pharmaceutical Scientists
1990	Fellow, American Association for the Advancement of Science
1996	Hallie Bruce Memorial Lecture Award
1997	Fellowship, Japanese Society for the Promotion of Science
1999	Meritorious Manuscript Award, American Association of Pharmaceutical Scientists
2001	Weaver Medal of Honor
2004	Distinguished Lecture, Creighton University School of Pharmacy and Health Professions
2005	Academy of Distinguished Teachers, University of Minnesota
2006	Distinguished Lecture, Temple University School of Pharmacy
2007	APhA Research Achievement Award in the Basic Pharmaceutical Sciences

COMMITTEE APPOINTMENTS

COLLEGE OF PHARMACY

1972-73, 1973-74	Student American Pharmaceutical Association Minnesota Chapter (Faculty Advisor)
1972-75	Student Admissions and Academic Standing Committee, College of Pharmacy
1972-73	Task Force on College of Pharmacy Organization
1973-74	Continuing Education Committee
1972-78	Admissions Committee for Pharm.D. Program, College of Pharmacy (Chair 1973-74; 1977-78)
1974-75	University of Minnesota Health Sciences B/C Implementation Committee
1974-77	Constitution and By-laws Committee
1974-75	Unit K Committee, Graduate School
1975-76	Task Force on Pharm.D. Admissions
1976-78	Professional Education Committee
1977-78	Task Force on Travel
1977-78	Anatomy, Physiology, Pathology Study Group
1977-78	Drug Product Design and Evaluation Study Group
1976-78	Search Committee for Biopharmaceutics Faculty Member
1977-78	Search Committee for Assistant Director HCMC

1977-78	Search Committee for Research Associate, CEP Project D-1 (Chairman)
1978-79	Pharm.D. Program Planning Committee (Chairman)
1978-79, 1979-80	Computer Systems Committee (Chairman)
1979-80	Professional Education Committee (Chairman)
1980-81	Educational Policy Committee (Chairman)
1980-82	Externship Committee
1981-82	Academic Standing Committee
1981-83	Health Sciences Policy and Review Council
1981-82	Graduate Faculty Nominations and Course Proposals Committee
1982-83	Academic Standing Committee (Chairman)
1982-83	Advisory Committee on Animal Care Facilities
1983-85	Council of Directors of Graduate Studies
1982-83	Task Force on Computers
1983	Search Committee for Department Chairman (Chairman)
1983	Search Committee for Clinical Faculty at HCMC
1984	Ad Hoc Committee on External Pharm.D. Program
1984	Executive Committee (Chairman)
1984	Search Committee for Dean of College of Pharmacy
1984	Search Committee for Psychiatry Position, St. Paul-Ramsey Medical Center
1984	Search Committee for Clinical Faculty at Hennepin County Medical Center
1985	Endowed Chair in Pharmaceutics Search Committee (Chair)
1985	Assistant Professor in Pharmaceutics Search Committee (Chair)
1985	Appointment, Promotion and Tenure Committee
1985	Space Committee
1985	Clinical Assistant Professor (MMC) Search Committee
1985-89	Executive Committee
1986-87	Appointment, Promotion and Tenure Committee (Chair)
1986-90	Educational Policy Committee
1986-87	Subcommittee of Educational Policy Committee
1986	Search Committee for Endowed Chair (Chair)
1986-87	College of Pharmacy Strategic Planning Committee
1986-87	Subcommittee of Strategic Planning Committee to Develop College Goals and Objectives
1987-90	Continuing Pharmacy Education Advisory Committee (Chair)
1987-88	Admissions Committee
1988-89	Admissions Committee (Chair)
1989-91	Promotion and Tenure Committee
1991-92	Promotion and Tenure Committee (Chair-Elect)
1991-92	General Research Support Committee
1992-93	Promotion and Tenure Committee (Chair)
1992-93	General Research Support Committee
1993-94	Academic Standing Committee (Chair-Elect)
1994-95	Academic Standing Committee (Chair)
1994-98	College Computer Committee
1995-96	Promotion and Tenure Committee
1995-96	Internal Organization and Leadership Task Force
1996-97	Nontraditional Pharm.D. Task Force
1997-98	Search Committee for Endowed Chair in Geriatric Pharmacotherapy
1997-98	Admissions Committee
1997-98	Search Committee for Immunotherapy Faculty Position (Chair)
1998-2000	Search Committee for Pharmaceutics Faculty Position
2000-2001	Educational Policy Committee
2001-2002	Search Committee for ECP Faculty Position
2001-2002	Educational Policy Committee (Chair)
2001-2002	Search Committee for Pharmaceutics Faculty Position
2001-2002	College of Pharmacy Phar. Sci. 2020 Committee, Capital Campaign (Co-Chair)

2001-2004	College of Pharmacy Faculty Consultative Committee
2002-2003	Educational Policy Committee (Past Chair)
2002-2003	College of Pharmacy Collegiate Review Committee (Chair)
2002-2003	College of Pharmacy Central Council (Faculty Representative)
2002-2003	College of Pharmacy Instructional Development Working Group for the Duluth Expansion
2003-2005	Search Committee for Pharmaceutics Faculty Position at UMD (Chair)
2004-2007	College of Pharmacy Assessment Committee
2005-2006	Search Committee for Endowed Chair in Geriatric Pharmacotherapy
2006-2007	Search Committee for Pharmaceutics Faculty Position

UNIVERSITY COMMITTEE APPOINTMENTS

1974-78	Subcommittee on Academic-Industrial Interface, Academic Relations Committee, 3M Technical Forum
1975-76	Health Sciences Primary Health Care Program Committee (Alternate), Solicitor for the University of Minnesota Consolidated Fund Drive
1977-78	Alternate Senator (U. of Minnesota)
1978-81	Senator (U. of Minnesota)
1984-85	Health Sciences Learning Resources Committee
1986	College Delegate to All-University Single Quarter Leave Working Group, Academic Affairs
1989	Health Sciences Policy and Review Council, Graduate School
1989-91; 1991-93	Biological Sciences (formerly Plant and Animal Sciences) Policy and Review Council, Graduate School
1991-93	Graduate Faculty Nominations Subcommittee, Biological Sciences Policy and Review Council, Graduate School
1992-93	Graduate Faculty Nominations Subcommittee (Chair), Biological Sciences Policy and Review Council, Graduate School
1995-1998	Biological Sciences Policy and Review Council, Graduate School
1997-98	Faculty Research Development Proposal Review Committee for the Academic Health Center
2001-2004	Academic Health Center Faculty Consultative Committee
2001-2002	SCFP Subcommittee on Twin Cities Facilities and Support Services (STCFSS)
2003	AHC Seed Grant Review Committee
2003	AHC FCC Internal Screening Committee for Academy of Excellence Nominees
2004-2007	All-University Honors Committee, University of Minnesota

STATE, NATIONAL, AND INTERNATIONAL COMMITTEE APPOINTMENTS

1974-76	Representative to AACP Council of Faculties
1977-78	AACP Task Force on Guidelines for Pharm.D. Accreditation
1980-82	Academic Advisory Committee, Kellogg Pharmaceutical Scientist Program
1981	Screening Committee for Academy of Pharmaceutical Sciences, Basic Pharmaceutics Section
1989-present	Member, Scientific Committee, International Pharmaceutical Technology Symposium (FIP)
1990	Academic Affairs Committee, AACP (Member)
1990	Program Committee, Controlled Release Society Annual Meeting (Member)
1989-91	Continuing Education Committee, State Board of Pharmacy (Member)
1990-95	USP Committee of Revision (Member)
1991-93	NIH/NINDS Antiepileptic Drug Development Program (Consultant)
1995	Fellows Nominations Committee for AAPS, PPDM Section
1995	Screening Committee for AAPS PPDM Section Abstracts
1997-2000	Fellows Nominations Committee for AAPS, PPDM Section
1999-2000	Committee on AAPS Section Structure and Procedure Guideline
2000-2001	PPDM Vice Chair, American Association of Pharmaceutical Scientists
2000-2002	Co-Chair, Organizing Committee, 3rd International Symposium on Microdialysis in Drug Research and Development

2001-2002	PPDM Chair Elect, American Association of Pharmaceutical Scientists
2001-2002	Annual Program Planning Committee, American Association of Pharmaceutical Scientists
2001-2002	Program Coordinating Committee, American Association of Pharmaceutical Scientists
2002-2003	PPDM Section Chair, American Association of Pharmaceutical Scientists
2002-2003	PPDM Committee for Graduate Student Symposium Awardees, American Association of Pharmaceutical Scientists
2002-2003	Short Course Program Review Team, American Association of Pharmaceutical Scientists
2003-2004	PPDM Section Past-Chair, American Association of Pharmaceutical Scientists
2004-2007	Member-at-Large, American Association of Pharmaceutical Scientists Executive Council
2004-2006	Clinical and Operational Working Group (CORWG), NASA
2004-2005	AAPS Executive Council Liaison to the Clinical Sciences section of AAPS
2005-2006	AAPS Executive Council Liaison to the DDD section of AAPS
2005-2006	AAPS Executive Council Liaison to the PDD section of AAPS
2005-2006	AAPS Executive Council Liaison to the 2006 Annual Meeting Program Committee
2005-2006	AAPS Executive Council Liaison to the 2006 Annual Meeting Screeners
2005-2006	AAPS Executive Council Liaison to the 2006 Program Coordination Committee
2006	AAPS Reference Resources Task Force
2006-2007	AAPS Executive Council Liaison to the APQ section of AAPS
2006-2007	AAPS Executive Council Liaison to the PT section of AAPS
2006-2007	AAPS Executive Council Liaison to the International Affairs Committee

INVITED PRESENTATIONS

Continuing Education Program (6 hours) Minneapolis, MN, 1973.
Upper Midwest Hospital Conference, 1974.
Continuing Education Program (6 hours) Rochester, MN, 1974.
University of Illinois, Chicago, IL, 1974.
Department of Clinical Pharmacology, University of Minnesota, 1974.
AACP Annual Meeting and Teachers' Seminar (Workshop Leader), Lake Kiamesha, NY, 1975.
Debate Symposium, "Drug Product Selection," St. Paul, MN, 1977.
Continuing Education for Minneapolis Veteran Pharmacists (2 hours), Minneapolis, MN, 1978.
Continuing Education in Pharmacy (2 hours), Mankato, MN, 1978
Continuing Education in Pharmacy "Seminar at Sea" (4 hours of instruction), 1978.
HPLC Workshop, Invited Lecturer, Bloomington, MN, 1978.
University of Kentucky, Lexington, KY, 1979.
American Association of Clinical Chemists, Midwest Section, Minneapolis, MN, 1979.
University of Illinois, Chicago, IL, 1979.
Smith Kline Corp., Philadelphia, PA, 1979.
Department of Pathology, St. Cloud Hospital, St. Cloud, MN, 1979.
Comprehensive Epilepsy Program, Minneapolis, MN, 1979.
University of North Carolina, Chapel Hill, NC, 1979.
Burroughs Wellcome Co., Research Triangle Park, NC, 1979.
St. Paul-Ramsey Medical Center, St. Paul, MN, 1989.
Continuing Education in Pharmacy (4 hours) Minneapolis, MN, September-October, 1981.
Medical Research Council of Canada, Visiting Professor, University of British Columbia, Vancouver, 1982.
Invited Lecturer, National Institutes of Health, Epilepsy Branch, Bethesda, MD, 1982.
Geriatric Research, Education and Clinical Center, Bloomington, MN, September, 1982.
Continuing Education in Pharmacy (6 hours), Duluth, MN, September, 1982.
Ciba-Geigy, Pharmaceuticals Division, Ardsley, December 2, 1982.
Swiss Federal Institute of Technology, Zurich, Switzerland, June 19, 1984.
Biopharmacy Division, Sandoz AG, Basel, Switzerland, June 22, 1984.
Biopharmacy Division, Sandoz AG, Basel, Switzerland, July 24, 1984.
"Cyclosporine Pharmacokinetics in the Rabbit: In Vivo Disposition and In Situ Absorption Studies," Rhone-Poulenc Visiting Professor, University of Toronto, Ontario, February 5, 1985.
"Pharmacokinetics and Pharmacodynamics," Drug Therapy Symposium VI, St. Paul, MN, February 27, 1985.

"Absorption and Disposition Studies with Cyclosporine," Sandoz, AG, Basel, Switzerland, July 15, 1985.

"Absorption of Cyclosporine from Rabbit Small Intestine Using an In Situ Perfusion Model," Vorstand des Instituts fur Pharmazie U. Lebensmittlechemie der Ludwig-Maximilians-Universitat, Munich, West Germany, July 17, 1985.

"Analytic considerations in the Investigation of the Pharmacokinetics of Cyclosporine," Medizinischen Hochschule, Hanover, West Germany, September 11, 1985.

"Mixed-Order Absorption of a Sustained Release Carbamazepine Tablet in Humans," Institut fur Pharmazeutische Technologie der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, West Germany, May 15, 1986.

"Simultaneous First- and Zero-order Absorption of Commercial Carbamazepine Tablets," 5th Symposium on Biopharmaceutics and Pharmacokinetics, Piestany, Czechoslovakia, May 22, 1986.

"Simultaneous First- and Zero-order Absorption of Tegretol in Human Volunteers," National Institutes of Health, Epilepsy Branch, NINCDS, Bethesda, MD, November 6, 1986.

"Comparison of Plasma AUCs using the Traditional Point-by-Point and Pooled Sample Methods: Application in the Analysis of Human Pharmacokinetics of Carbamazepine and its metabolites," Food and Drug Administration, Rockville, MD, July 20, 1987.

"Pharmacokinetics in Contemporary Pharmacy Practice," Minneapolis Veteran Pharmacists Association, Richfield, MN, September 15, 1987.

"The Absorption and Disposition Kinetics of Carbamazepine and its Metabolites in Humans," Ciba-Geigy, Summit, NJ, July 23, 1987.

The following four lectures were given in Beijing, Chengdu, and Guilin, China during a visit sponsored by the Chinese Academy of Medical Sciences in late October/early November 1987:

1. "Theory and Application of a Pharmacokinetic Model in Individualizing Dosing Regimens for the Aminoglycosides."
2. "First- and Zero-order Absorption of Carbamazepine from Commercial Tablets in Epileptic Patients and Normal Volunteers."
3. "Significance of Nonlinear Disposition Kinetics in the Adjustment of Dosing Regimens."
4. "Relative Bioavailability of Phenytoin Formulations: Problems in Assessment Due to Michaelis-Menten Elimination Kinetics."

"Does Tegretol need to be Dosed TID?" Comprehensive Epilepsy Program, Minneapolis, MN, March 21, 1988.

"The Kinetics of Absorption of Carbamazepine (Tegretol) and its Metabolism in Humans," Vorstand des Instituts der Pharmazie, Ludwig-Maximilians Universitat, Munich FRG, June 8, 1988.

"Pharmacokinetic and Physiologic Considerations in Oral Controlled Drug Delivery," Novel Drug Delivery Symposium, Minneapolis, MN, September 20, 1988.

"Clinical Applications of the Two-Compartment Open Model," Regional Kidney Disease Program, Hennepin County Medical Center, Minneapolis, MN, November 16, 1988.

The following five lectures were presented in a Continuing Education in Pharmacy Program: "Concepts and Applications in Pharmacokinetics, Parts I and II"; "Therapeutic Response and Toxicity"; "Monitoring Drug Therapy"; and "Bioavailability and Bioequivalence", St. Thomas, Virgin Islands, March 8-13, 1989.

"The Pharmacokinetics of Zidovudine (AZT) with Some Observations on the Interaction with Probenecid," Queen's University of Belfast, Belfast, North Ireland, June 15, 1989.

"Pharmacokinetic and Analytical Considerations in Monitoring Zidovudine (AZT) Levels in Children with Aids," Fourth International Congress on Pediatric Laboratory Medicine, Washington, DC, August 23, 1989.

"Inhibition of Zidovudine Metabolism and Excretory Transport," Department of Pharmacodynamics, Semmelweis University of Medicine, Budapest, Hungary, September 13, 1989.

"Evaluating Bioequivalence," Western Michigan Society of Hospital Pharmacists, Grand Rapids, MI, March 2, 1990.

"Effect of Temperature and Medium of Analysis on Cyclosporine Concentration," Canadian Consensus Meeting on Cyclosporine Monitoring, Minaki Lodge, Canada, May 11, 1990.

"Studies of the Interaction between Zidovudine (AZT) and Probenecid in Animals and Humans." Pharmaceutics and Process R & D, Ayerst Laboratories Inc., Rouse's Point, NY, August 17, 1990.

"Mechanistic Studies to Examine the Effect of Probenecid on the Brain Uptake of Zidovudine," Shanghai Medical University, Shanghai, P.R.C., October 13, 1990.

A lecture series (16 hrs) on the topic of "Clinical Pharmacokinetics and Therapeutic Drug Monitoring" was given to staff members of the Chinese Academy of Medical Sciences and Hospital Pharmacists, Beijing, P.R.C., October 15-20, 1990.

"Comparative Intestinal Absorption of Compounds of Varying Lipophilicity, and the Effect of Absorptive Water Flux." Lederle Laboratories, Pearl River, NY, September 12, 1991.

"Analysis of Zidovudine Distribution into Specific Brain Regions Utilizing Microdialysis," Bristol Myers-Squibb Research Institute, Princeton, NJ, September 17, 1991.

"Distribution of AZT Into Specific Brain Regions in the Rabbit Utilizing Microdialysis," University of Illinois College of Medicine, Peoria, IL, October 9, 1991.

"Studies on the Transport of Nucleosides into Specific Brain Regions Using Microdialysis with *In Vivo* Calibration." University of Florida, College of Pharmacy, Gainesville, FL, December 6, 1991.

"Analysis of Zidovudine Distribution into Specific Brain Regions Utilizing Microdialysis," University of Arizona College of Pharmacy, Tucson, AZ, February 17, 1992.

"Regional Considerations in the In Situ Intestinal Absorption of Glycylcycline and Minocycline, and the Effect of Solvent Drag," Lederle Laboratories, Pearl River, NY, May 11, 1992.

"Comparative Absorption of Fluorothymidine and Related Nucleosides in Different Anatomic Intestinal Regions," Lederle Laboratories, Pearl River, NY, May 11, 1992.

"Microdialysis Techniques for the Study of Drug Distribution, and the Problem of Recovery *In Vivo*," Europhor Toulouse, France, June 19, 1992.

"The Use of Microdialysis in Studying the Distribution of Exogenous Substances in Biological Tissues," Sandoz Pharma, Basel Switzerland, June 24, 1992.

"Inhibition of Brain Distribution and Systemic Clearance of AZT by Probenecid," Sandoz Pharma, Basel Switzerland, June 30, 1992.

"Uptake of Zidovudine (AZT) into Rabbit Brain Using Microdialysis with *In Vivo* Calibration," Knoll AG, Ludwigshafen, Germany, July 1, 1992.

"Microdialysis in the Study of the Distribution and Metabolism of Exogenous Substances," Pharmaceutical Chemical Institute, University of Heidelberg, Heidelberg, Germany, July 2, 1992.

"The Relationship Between Urine and Plasma Concentrations of Lipophilic Drugs: Implications for Therapeutic Drug Monitoring," Sandoz Pharma, Basel Switzerland, July 8, 1992.

"Estimation of the Elimination Rate Constant for Metabolites which Exhibit Formation-Rate Limited Disappearance," Sandoz Pharma, Basel Switzerland, July 23, 1992.

"Experimental Determination of Free Tissue Levels Using Microdialysis," 4th Biennial Conference on Chemotherapy of Infectious Diseases and Malignancies, Prague, Czechoslovakia, August 31, 1992.

"*In Situ* Intestinal Absorption of Tetracycline Derivatives and the Effect of Absorptive Water Flux," Lederle Laboratories, Pearl River, NY, November 13, 1992.

"Reversibility of Carbamazepine Autoinduction upon Dose Termination in Normal Volunteers," Abbott Laboratories, Abbott Park, IL, December 2, 1992.

"Barriers to the Oral Delivery of Drugs," Wyeth-Ayerst Research, Radnor, PA, February 23, 1993.

"Preliminary Results of Studies which Examine the Distribution of the NMDA Antagonist, EAB 515, to Rat Brain," Sandoz Pharma, Basel Switzerland, April 26, 1993.

"Microdialysis Calibration Using the Zero-Net Flux Method and Retrodialysis in Studying the Distribution of Exogenous Substances to Rat Brain," Sandoz Pharma, Basel Switzerland, April 26, 1993.

"Investigation of the Pharmacodynamics of the NMDA Antagonist, EAB 515, in the Rat During Intravenous and Intracerebroventricular Administration." Sandoz Research Institute, Berne, Switzerland, April 28, 1993.

"Comparative Distribution of AZT to Brain Tissue Extracellular Fluid During Intravenous and Intracerebroventricular Infusion." Food and Drug Administration, Rockville, MD, May 21, 1993.

"Interspecies Scaling of Pharmacokinetics in the Evaluation and Development of New Antiepileptic Drugs." Natural Resources Research Institute, University of Minnesota—Duluth, Duluth, MN, August 11, 1993.

"Application of Pharmacokinetic Principles in Practice." Minneapolis Veteran Pharmacists Association, St. Louis Park, MN, September 21, 1993.

"Microdialysis as a Tool to Study Drug Delivery to the Brain." North Jersey American Chemical Society Drug Metabolism Discussion Group, Somerset, NJ, October 7, 1993.

"Graduate Studies and Research Careers in Pharmaceutics." University of Minnesota—Duluth Department of Chemistry, Duluth, MN, December 3, 1993.

"Microdialysis in Pharmacokinetic and Drug Metabolism Studies." 95th Annual Meeting, American Society for Clinical Pharmacology and Therapeutics, New Orleans, LA, April 1, 1994.

"Modeling and Simulation of Complex Pharmacokinetic Systems." NATO Advanced Study Institute, Erice, Italy, April 12, 1994.

"Microdialysis in the Study of Drug Distribution." NATO Advanced Study Institute, Erice, Italy, April 13, 1994.

"Pharmacokinetic Studies Utilizing Microdialysis." Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS, May 2, 1994.

"Pharmacokinetic Studies Utilizing Microdialysis and On-Line HPLC." 4th International Workshop in Bioanalysis, Lawrence, KS, July 12, 1994.

"Application of Microdialysis in Pharmacokinetic Studies." Gordon Research Conference in Drug Metabolism, Holderness School, Plymouth, NH, July 20, 1994.

"Microdialysis and its Application in Pharmacokinetic Studies." Ciba-Geigy, Pharmacokinetics and Bioanalytics Division, Ardsley, NY, July 25, 1994.

"Assessing Drug Transport in the Brain with Microdialysis." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

"Applications of Microdialysis in Preclinical Pharmacokinetic Studies." 3M Pharmaceuticals, 3M Center, St. Paul, MN, November 29, 1994.

"Problems in Assessing the Absorption of Carbamazepine from Sustained Release Dosage Forms in Epileptic Patients." Pharmavene, Inc., Gaithersburg, MD, February 23, 1995.

"Selected Preclinical Pharmacokinetic Studies with Tacrine." Parke-Davis Pharmaceuticals, Ann Arbor, MI, May 5, 1995.

"Brain Distribution and Metabolism Studies with Tacrine and Two Hydroxylated Metabolites." Department of Pharmaceutics and Pharmacodynamics, University of Illinois, Chicago, IL, July 28, 1995.

"Microdialysis and its Application in Preclinical Drug Distribution and Absorption Studies." Chiron Corporation, Emeryville, CA, August 18, 1995.

"The Principle of Quantitative Microdialysis and its Application in Preclinical Drug Distribution Studies." Genentech, Inc., South San Francisco, CA, October 9, 1995.

"Graduate Programs and Research Opportunities in Pharmaceutics." 13th Annual Symposium on Pharmaceutical Sciences Graduate Programs, Merrillville, IN, October 21, 1995.

"Principles of Microdialysis and Applications in Preclinical Drug Distribution and Absorption Studies," Wyeth-Ayerst, Pearl River, NY, December 6, 1995.

"Microdialysis in Preclinical Drug Distribution Studies." Dupont Merck, Newark ,DE, December 8, 1995.

"Microdialysis and its Application to the Study of Drug/Metabolite Distribution in the Central Nervous System," University of Pittsburgh, Pittsburgh, PA, January 25, 1996.

"Therapeutic Drug Monitoring: A Fodor's Guide." Hallie Bruce Memorial Lecture Award, Minnesota Society of Health-Services Pharmacists, Minneapolis, MN, April 13, 1996"

"Preclinical Studies of Drug Distribution to the Brain using Microdialysis." Pharmaceutical Peptides Inc, Cambridge, MA, May 2, 1996.

"Microdialysis and its Application in Nonclinical Studies of Drug Distribution and Absorption." Bristol-Myers Squibb, Pinceton, NJ, June 24, 1996.

"Continuous Monitoring by Microdialysis in Neuropharmacokinetic Investigations." Faculty of Pharmacy, University of Tanta, Tanta, Egypt, March 5, 1997.

"Preclinical Studies of Drug Distribution to the Brain using Microdialysis," Toyama Medical and Pharmaceutical University, Toyama, Japan, April 11, 1997.

"Application of Pharmacokinetic Principles in Individualizing Aminoglycoside Dosing," Toyama Medical and Pharmaceutical University, Toyama, Japan, April 11, 1997.

"Preclinical Studies of Drug Distribution to the Brain using Microdialysis," Meiji College of Pharmacy, Japan, April 18, 1997.

"Individualizing Aminoglycoside Dosing and Once-a-Day Aminoglyocosides," Meiji College of Pharmacy, Japan, April 18, 1997.

"Education of Pharmacists and Pharmaceutical Scientists at the University of Minnesota," 260th Meeting on Continuing Education of Pharmacists, Okuda-Shinmachi, Toyama, Japan, April 26, 1997.

"Pharmacokinetic Basis of Drug-drug Interactions," Novartis Workshop on Metabolic Drug-Drug Interactions, Schluchsee, Germany, October 14, 1997.

"Microdialysis and its Application in Preclinical Pharmacokinetic Studies," Merck Research Laboratories, West Point PA, December 16, 1997.

"Microdialysis and its Application in Preclinical Pharmacokinetic Studies," Merck and Co, Inc. Rahway NJ, December 17, 1997.

"Brain Distribution Studies employng Microdialysis and Crossover Designs," *1st International Symposium in Drug Research and Development*, Noorwijkerhout, Netherlands, April 3, 1998.

"Application of Sample Pooling in the Time Domain to Estimate CL, Vss and MRT in the Search for Lead Compounds." Chiron Corporation, Emeryville, CA, May 5, 1998.

"Microdialysis as a Sampling Technique in Preclinical Pharmacokinetic Studies." Pfizer Inc, Groton CT, June 18,1998

"Assessing Drug Delivery to the CNS Using Microdialysis Sampling." School of Medicine, University of Minnesota, Duluth, October 19,1998.

"Pharmacokinetic Studies Using Microdialysis Sampling." American Association of Pharmaceutical Scientists Annual Meeting, San Francisco CA, November 18, 1998.

"Applications of Microdialysis in Pharmacokinetics: Brain, Blood, and Middle Ear Fluid." Bristol-Myers Squibb, Wallingford CT, May 14, 1999.

"Applications of Microdialysis in Preclinical Pharmacokinetics: Brain, Blood and Middle Ear Fluid." Parke-Davis, Ann Arbor, MI, May 21, 1999.

"Blood Sample Pooling and the Determination of Mean Residence Times in High-Throughput Pharmacokinetic Screening"." Parke-Davis, Ann Arbor, MI, May 21, 1999.

"Role of controlled release formulations in the steady-state pharmacokinetics and pharmacodynamics of anticonvulsants" Impax Pharmaceuticals, Inc, Hayward CA, June 9, 1999.

"Investigating Neuropharmacokinetics and Drug Delivery to the CNS using Microdialysis." *8th International Conference on In Vivo Methods: Monitoring Molecules in Neuroscience.* Stony Brook NY, June 19-23, 1999.

"Use of Microdialysis in Pharmacokinetics" at the 8th BMSR Workshop on *Advanced Methods of Pharmacokinetic and Pharmacodynamic System Analysis*, Marina del Rey, CA June 25-26, 1999.

"Applications of Microdialysis in Preclinical Pharmacokinetics." Amgen, Inc., Thousand Oaks, CA, June 28, 1999.

"Pharmacokinetic –Pharmacodynamic Principles in Drug Development." Chiron Corporation, Emeryville, CA, August 20, 1999.

"Microdialysis and its Application in Pharmacokinetics: Brain, Blood, and Middle Ear Fluid." Abbott Labs, Abbott Park IL Aug 27, 1999.

"Distribution kinetics of antibiotics to the chinchilla middle ear" Department of Biopharmaceutical Sciences, Uppsala University, Uppsala, Sweden, March 16, 2000

"In Vivo Microdialysis as a Tool to Study Site Specific Drug Delivery" *Millennial World Congress of Pharmaceutical Sciences.* San Francisco CA, April 17, 2000

"In Vivo Microdialysis as a Tool to Study Site Specific Drug Delivery" *Engebretson Symposium on Drug Discovery and Development.* Minneapolis, MN. May 18, 2000

"In Vivo Microdialysis as a Tool to Study Drug Delivery". *19th Annual Robert S. Rozman Memorial Symposium,* Langhorne PA , May 25, 2000

"Basic Principles of Microdialysis, Experimental Setup". *Course on Basic and Advanced Aspects of In Vivo Microdialysis*", Stockholm, Sweden, June14, 2000.

"Recovery: Basic Idea and Practical Methods". *Course on Basic and Advanced Aspects of In Vivo Microdialysis*", Stockholm, Sweden, June14, 2000.

"Studies of Distribution of Antibiotics to the Middle Ear by Microdialysis" *2nd International Symposium on Microdialysis in Drug Research and Development*, Stockholm, Sweden, June15, 2000.

"Basic Concepts in Clinical Pharmacokinetics" A 2-Day Course. Abbott Laboratories, Abbott Park IL and Victory Hospital, Waukegan, IL, July 18-19, 2000

"Microdialysis and its Application in Preclinical Pharmacokinetics: Brain, Blood, and Middle Ear Fluid." Dupont Pharmaceuticals, Wilmington, DE July12, 2000.

"Pharmacokinetic –Pharmacodynamic Principles in Drug Development." Abbott Labs, Abbott Park IL Jan 9, 2001

"Biopharmaceutical and Pharmacokinetic Considerations in Delivering Drug to the CNS" Medtronic Neuro Division, Minneapolis. January 25, 2001

"Clinical Pharmacokinetic Principles in Drug Development." Novartis Pharma, Tokyo, April 12, 2001

"In Vivo Microdialysis as a Tool to Study Site Specific Drug Delivery" Showa University, Tokyo, Japan, April 13, 2001

"In Vivo Microdialysis as a Tool to Study Drug Delivery in Preclinical Studies". Xi'an Medical College, Xi'an, PRC. April 25, 2001

"Principles of Pharmacokinetics and their Application in Drug Development" Novartis Pharma, Basel, Switzerland, July 3, 2001.

"Microdialysis and its Application in Preclinical Studies of Drug Delivery to Target Tissues" Boehringer-Ingelheim Pharma KG, Dept. of Pharmacokinetics & Drug Metabolism, Biberach, Germany, July 5, 2001.
"Estimation of Intrinsic Clearances and Organ Partition Coefficients in an Organ Perfusion Model" Novartis Pharma, Basel, Switzerland, July 26, 2001.
"Pharmacodynamic Modeling of the Sigmoid Emax Model" Novartis Pharma, Basel, Switzerland, July 31, 2001.
"Prediction of the Pharmacokinetics of Cefdinir in Children from the Results of Animal Studies. Omnicef® Clinical Advisory Meeting, Dallas, TX, February 9, 2002.
"Applications of Microdialysis in Studying Drug Delivery to Specific Targets". Guilin Medical School, Guilin PRC, March 28, 2002
"Microdialysis: A Tool to Study Brain Uptake?" Gordon Research Conference on the Barriers of the CNS, Tilton School, Tilton NH, June 25, 2002
"A Model for the Distribution of Drugs between Plasma, CSF and Parenchyma", Workshop on Microdialysis Techniques in the CNS, Gordon Research Conference on the Barriers of the CNS, Tilton School, Tilton NH, June 26, 2002
"Microdialysis in the Study of Drug Delivery to the Central Nervous System", Department of Pharmaceutics, Seoul National University, Seoul, South Korea, November 25, 2002.
"Investigating Antibiotic Delivery to the Middle Ear". Chong Kun Dang Pharma, Cheonan, South Korea, November 27, 2002
"Microdialysis and its Application in Preclinical Pharmacokinetic and Drug Delivery Investigations", 32nd Annual Meeting of the Korean Pharmaceutical Society, Seoul, South Korea, November 28, 2002.
"Applications of Pharmacokinetic Principles in Drug Development". Schering-Plough Research Institute. Kenilworth, NJ. December 19, 2002
"A Course in Pharmacokinetics in Pharmaceutical Development". Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. May 15-16, 2003
"Characterizing Antibiotic Delivery to the Middle Ear for the Treatment of Otitis Media. Biomedical Simulations Resource Workshop: Advanced Methods of PK/PD Systems Analysis. Marina del Rey, CA. June 20-21, 2003.
"Cerebrospinal Fluid Distribution of Intrathecally Administered Antiviral Nucleosides". Monitoring Molecules in Neuroscience. 10th International Conference on In Vivo Methods. Department of Neuroscience, Karolinska Institutet Stockholm, Sweden. June 24-27, 2003
"Microdialysis Sampling in Drug Development: Applications in Preclinical Research." Sunrise School, American Association of Pharmaceutical Scientists Annual Meeting, Salt Lake City, UT, October 26, 2003.
"Clinical Pharmacokinetics in Pharmaceutical Development." Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. July 23-24, 2003.
"Microdialysis Sampling in Drug Development: Applications in Preclinical Research." Sunrise School, American Association of Pharmaceutical Scientists Annual Meeting, Salt Lake City, UT. October 26, 2003.
"The Role of Pharmacokinetics in Drug Discovery." Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. March 18, 2004.
"Microdialysis and its Application in Preclinical Pharmacokinetic and Drug Delivery Investigations." CDER, Food and Drug Administration, Rockville, MD. March 29, 2004.
"Interspecies Scaling, PB-PK modeling and Microdialysis in Antibiotic Drug Development." Novartis Institute for Biomedical Research, Cambridge, MA. April 9, 2004.
"Does it get to the Target Site? Microdialysis as a Tool to Study Preclinical Drug Distribution and Delivery" Amgen Inc., Thousand Oaks, CA. April 30, 2004.
"Preclinical Pharmacokinetics in Pharmaceutical Discovery." Bristol-Myers Squibb, Princeton, NJ. May 6-7, 2004.
"Microdialysis of Antibiotics." 4th International Symposium on Microdialysis in Drug Research and Development, Vienna, Austria, June 19, 2004.
"The Chinchilla Microdialysis AOM Model" Pfizer Global Pharmaceuticals, New York, NY. June 25, 2004.
"Advantages of the Chinchilla Microdialysis Model" Scientific Basis for Tissue-Directed Antimicrobial Therapy Symposium, Boston MA, July 21-22, 2004.

"Evaluating Drug Distribution to the Target Site and Predicting Tissue Exposure in Humans from Animal Data" Scientific Advisory Committee, Abbott Laboratories. The FDA Critical Path Initiative and the Role of Modeling/Simulation in Improving the Efficiency of Drug Development. Lake Forest, IL. September 8-9, 2004.

"Assessing Drug Delivery to the Target Site: The Role of Microdialysis in Measuring Tissue Exposure in Animals and Humans." Distinguished Lecture, Creighton University School of Pharmacy and Health Professions, Omaha NE, November 30, 2004.

"Microdialysis—Introduction to Basic Principles and Applications". AAPS Workshop on Microdialysis Principles, Application, and Regulatory Perspectives, Nashville TN, November 4, 2005.

"An Introduction to Pharmacokinetics for Pharmaceutical Scientists". Gilead Pharmaceuticals, Foster City, CA. December 8-9, 2005.

"A Phase I Open-Label, Dose-Ranging Study to Investigate the Safety and Tolerability of Gabapentin Injection Administered Intrathecally in Individuals with Chronic, Intractable Pain: A Pharmacokinetic Report". Medtronic WHQ, Fridley, MN, February 16, 2006.

"Public Outreach and AAPS: Students are the Future of Our Association". Temple University School of Pharmacy, Philadelphia, PA. February 20, 2006.

"Assessing Drug Delivery: Using Microdialysis to Measure Target Site Exposure in Animals and Humans". Wyeth Distinguished Lecture Series, Temple University School of Pharmacy, Philadelphia, PA. February 20, 2006.

"Pharmacokinetics for Scientists Engaged in Drug Discovery". Lundbeck Research, USA. Paramus NJ. February 24, 2006.

"Pharmacokinetic Issues related to Intrathecal Drug Dosing". Medtronic WHQ, Fridley, MN, March 15, 2006.

"TTM Technology: Antibiotic Distribution to Middle Ear Fluid" Abbott Laboratories, Abbott Park, IL. May 16, 2006.

"Transtympanic Membrane (TTM) Drug Delivery to the Middle Ear" Alcon Laboratories, Fort Wiorth TX. Feb 2, 2007.

"Bugs and Drugs: Does the Anti-infective Agent get to the Target Site?". Science Lunceon Presentation. APhA Annual Meeting. Atlanta, GA. March 18, 2007

"Exploring Anti-infective Agents with Microdialysis" Keynote Address. Fifth International Symposium on Microdialysis in Drug Research and Development. Leiden, NE. April 25, 2007.

TEACHING

Undergraduate

1971 - 1972	Co-instructor in Phar 5680 "Pharmacokinetics"
1971 - 1975	Discussant in Pharm.D. Conferences
1972 - 1973	Participating instructor in Phar 5670
1972 - 1978	Discussion leader in Pharm.D. I conferences
1972 - 1985	Course director, Phar 5680 "Pharmacokinetics"
1975 - 1995	Course director, Phar 5685 "Clinical Pharmacokinetics"
1991 - 1999	Course director, Phar 5681 "Basic Pharmacokinetic Modeling"
1996 - 1998	Course director and Participating instructor, Phmc 5460 "Pharmacokinetics"
1998.– 2003	Course director and instructor, Phar 6216 "Pharmacokinetic Simulation and Data Analysis using SAAM "
1999 - 2004	Course director and Participating instructor, Phar 6163 "Pharmacokinetics"
1998 - 2004	Participating instructor in Phar 6164 "Biopharmaceutics"
2004 - present	Participating instructor, Phar 6163 "Pharmacokinetics"

Graduate

1972 - 1999	Course director in Phm 8420 "Modeling Approaches in Pharmacokinetics" participating instructor in Phm 8421, Phm 8425
1972 - present	Participating instructor in Phm 8100 (Seminar) and Phm 8101 (Pharmaceutics Readings)
1984 - 1999	Participating instructor in Phm 8425 "Advanced Topics in Pharmacokinetics"
1986 - 1999	Course co-director in Phm 8105 "Pharmacokinetics Research Seminar"
2000 - present	Course co-director in Phm 8150 "Pharmacokinetics Research Seminar"
2000 - present	Course Co-director and Participating instructor in Phm 8421 "Advanced Pharmacokinetics"
2004 - present	Participating instructor in Phm 8481 "Advanced Neuropharmaceutics"

Graduate Students Advised:

1978	Wargin, W.A.	Ph.D.
1978	El-Yazigi, A.	Ph.D.
1980	Mugure Pyron	M.S.
1981	Sue-Chi Wu	M.S.
1983	Hsuehling Su	M.S.
1984	Dale Yu	Ph.D.
1984	Walid Awni	Ph.D.
1985	Lillian Riad	M.S.
1985	Rose Eggerth	Ph.D.
1987	Hisham Abou-Auda	Ph.D.
1989	Mohsen Hedaya	Ph.D.
1989	Ajit K. Shah	Ph.D.
1989	Lillian Riad	Ph.D.
1991	Helen Chan	Ph.D.
1992	William Elmquist	Ph.D.
1992	Shekman Wong	Ph.D.
1994	Yanfeng Wang	Ph.D.
1994	Bimal Malhotra	Ph.D.
1996	Richard Brundage	Ph.D.
1997	Zheng Yang	Ph.D
1998	Belinda Cheung	Ph.D.
2001	Yue Huang	Ph.D
2001	Guanfa Gan	Ph.D.
2002	Joanna Peng	Ph.D
2002	Tong Zhu	Ph.D.
2004	Ji Ping	Ph.D
2004	Wei Liu	Ph.D.
2005	Yan Song	Ph.D.
2007	Nael Mostafa	Ph.D.
2007	Zhihong Li	Ph.D.

GRANTS , CONTRACTS, and OTHER SUPPORT

1972-73	University of Minnesota Graduate School
1973-74	University of Minnesota Media Production Fund
1975-78; 1978-80	NIH/NINCDS Comprehensive Epilepsy Program Contract (Principal Investigator, Project D-1)
1976; 1977	Medical Education and Research Foundation Grant (Co-investigator with John W. McBride, M.D.)
1976-78	FDA Contract to Study the Pharmacokinetics and Toxicology of Phenytoin Sodium Products in Clinical Patients
1980-81; 1981-83	Grant to Support Research Involving the Analysis of Cyclosporin A in Biological Fluids (Sandoz, Inc.)
1982-83; 1983-84	"Pharmacokinetics and Biopharmaceutic Studies of Cyclosporin A in Selected Animal and *In Vitro* Systems" (NIH; Principal Investigator; Co-investigator, R.P. Enever)
1984	Comparative Bioavailability of Sodium Phenytoin in Normal Volunteers (Zenith Labs)
1984	Relative Bioavailability of Carbamazepine in Chewable and Conventional Tablets (Ciba-Geigy)
1984	Transdermal Delivery of Propranolol (Medtronics)
11/84 - 1/85	Absorption and Metabolism of Carbamazepine in Normal Volunteers (Ciba-Geigy)
1/85 - 4/85	Transdermal Absorption of β-Blockers (Medtronics, Inc.)
11/85 - 4/86	Relative Bioavailability of Sustained Release Oral Dosage Forms of Carbamazepine (Ciba-Geigy)
1/86 - 6/86	Analysis of Analgesics in Receptor Media (Medtronics)
8/86 - 12/86	Bioequivalence of Carbamazepine Oral Dosage Forms (Ciba-Geigy)
1/86 - 12/88	Pharmacokinetics of Diltiazem in the Rabbit (Marion)
2/87 - 9/87	Bioequivalence of Carbamazepine Dosage Forms Demonstrating Varying Dissolution Rates (Ciba-Geigy)
6/1/87 - 10/15/87	Effect of Urine Flow on the Renal Clearance of Carbamazepine and its Metabolites in Humans (Ciba-Geigy)
1/88 - 6/88	Effect of Fasting on the Absorption of Diclofenac Sodium in Normal Human Volunteers (Ciba-Geigy)
4/1/89 - 3/31/92	Enhancing Brain Uptake of AZT by Transport Inhibition, (NINCDS / NIH)
7/1/89 - 6/30/90	Induction of Carbamazepine Metabolism as a Function of Dosing Rate in Normal Volunteers (Ciba-Geigy)
9/91 - 6/92	Brain Distribution of EAB-515 in the Rabbit (Sandoz, Ltd.)
11/91 - 5/92	*In Situ* Absorption from Rabbit Intestine (Lederle Laboratories)
3/92 - 8/92	Clinical Studies of the Absorption of an Oral Immunosuppressant (Apotex Laboratories)
11/92 - 10/93	Brain Distribution of an NMDA-Receptor Antagonist in the Rat (Sandoz, Ltd).
10/92 - 5/93	Brain Uptake of a CNS-Active Agent (Warner-Lambert)
11/92 - 3/93	*In Situ* Absorption from Rabbit Intestine (Lederle Laboratories)
9/94 - 5/95	Population Pharmacokinetic Analysis of A General Anesthetic in Man (Abbott Laboratories)
7/94 - 5/95	Brain Uptake of a Cholinesterase Inhibitor and its Metabolites (Warner-Lambert)
10/94 - 9/95	Distribution of Antiviral Nucleosides into Rat Cortex (Bristol-Myers Squibb)
9/95 - 8/96	Bioanalytical Methods Development of Selected Drugs and Metabolites (MedTox)
1/96-9/96	Pharmacokinetic Analysis of IL-2 in the Pig (Chiron)
1/96 - 6/98	Analysis of Selected Macrolides by High-pressure Liquid Chromatography (TAP)
4/96-10/97	Brain Penetration of Fosphenytoin and Phenytoin in the Rabbit (Warner-Lambert)
4/96-9/96	Analysis and Brain Uptake of PPI-457 (Pharmaceutical Peptides, Inc)
7/97-3/98	Regional Intestinal Absorption of Anti-CMV agents (Bristol-Myers Squibb)
8/97-6/98	EM574 absorption in the rabbit in situ (TAP)
7/97-9/97	Pharmacokinetics of macrolides in Protocol EM-97-006 (TAP)
11/97-12/97	Drug Interaction Pharmacokinetic Analysis (McNeil)
8/97-3/98	Analysis and Pharmacokinetics of Macrolides in EM-97-008 (TAP)
10/97-12/97	Pharmacokinetics of Slow Release Agents in the CNS (Chiron)
1/98	LC/MS/MS Equipment Grant (TAP)

2/98-12/99	Analysis of Macrolides and Metabolites in EM-97-013 (TAP)
3/98-12/99	Chemical Stability of Selected Agents (Medtronic)
5/98	Validation of Analysis of Macrolides in Dog Plasma (TAP)
8/98	Validation of Analysis of Macrolides in Rabbit Plasma (TAP)
8/98	Stability of anticancer drugs in solution (Medtronic)
8/98	EM574 toxicokinetics in the dog (TAP)
12/98	EM574 toxicokinetics in the rabbit (TAP)
1/99	Pharmacodynamics of EM574 on LES Pressure (protocol 004) (TAP)
3/99	Effect of Time of Dosing on Absorption of EM574 (protocol 007(TAP)
4/99	Effect of Gastric Emptying on the pharmacokinetics of EM574 and its metabolites (protocol 002) (TAP)
2/9	Stability of FUDR and heparin in solution (Medtronic)
2/99	Pharmacodynamics and PKs of EM574 and its metabolites during chronic dosing (protocol 029) (TAP)
3/00-8/01	Pharmacokinetics of CDTR and distribution to middle ear fluid (TAP)
8/00-6-01	Distribution of ketolides to middle ear fluid (Abbott)
10/01-09/03	Pharmacokinetics of Ketolides (Abbott)
12/01-11/03	Pharmacokinetics and Distribution of cefdinir (Abbott)
12/02-12-03	Effect of a P-Glycoprotein Inhibitor on the Middle Ear Distribution of Clarithromycin (Abbott)
12/02-6-04	Distribution a Cephalosporin into Middle Ear Fluid in Children with Otitis Media (H LaRoche)
12/02-12-04	Development and Testing of Formulations for Delivery of Antibiotics to the Middle Ear (Abbott)
5/03-4/05	A New Approach for the Therapy of Otitis Media (Abbott)
8/04-7/05	Distribution of Macrolide antibiotics to tissue sites (Pfizer)
5/05-11/05	Testing the Distribution of Amoxicillin into Middle Ear Fluid in the Chinchilla following Pulsatile Dose Administration (Advancis)
1/06-9-06	Distribution of Macrolide antibiotics to pulmonary tissue and skeletal muscle (Pfizer)

PATENT FILED

"METHODS AND COMPOSITIONS FOR APPLYING PHARMACOLOGIC AGENTS TO THE EAR." UMN Docket # Z01159. RJ Sawchuk and BW Cheung Filing Date: 11/27/02; #06,306,517

PUBLICATIONS

BOOKS AND CHAPTERS

J. Blanchard, R.J. Sawchuk and B.B. Brodie, Editors. Principles and Perspectives in Drug Bioavailability. S. Karger, Basel, 1979.

J. Blanchard and R.J. Sawchuk, "Drug Bioavailability: An Overview" in Principles and Perspectives of Drug Bioavailability, J. Blanchard, R.J. Sawchuk and B.B. Brodie (Editors), S. Karger, Basel, 1979.

I.E. Leppik, J. Shope, R.J. Sawchuk, W.A. Hauser and B. Van Dyne, "Variability of Antiepileptic Drug Levels During Chronic Therapy" in Epileptology, M. Dam, L. Gram and K. Penry (Editors), Raven Press, NY, 1981.

R.J. Sawchuk, "Drug Absorption and Disposition in Burn Patients" in The Pharmacokinetic Basis of Drug Treatment, N. Massoud, L.Z. Benet, and J.G. Gambertoglio (Editors), Raven Press, NY, 1984.

"Use of Microdialysis in Drug Delivery Studies." Theme Issue. W.F. Elmquist and R.J. Sawchuk (Editors) *Advanced Drug Delivery Reviews* 45, Nos. 2-3 (2000).

R. J. Sawchuk and B.W.Y. Cheung, "Application of Microdialysis in Pharmacokinetic Studies." in Handbook of Microdialysis: Methods, Applications and Clinical Aspects, B.H.C. Westerink and T.I.F.H. Cremers (Editors), Academic Press, Amsterdam, 2007.

PROFESSIONAL PUBLICATIONS

R.J. Sawchuk, "The Plateau Principle in Drug Therapy. Part 1: The Principle and Its Application." *Minn. Pharmacist* 27(6): 19 (1973).

R.J. Sawchuk, "The Plateau Principle in Drug Therapy. Part 2: Factors Governing Plateau Levels During Chronic Drug Therapy." *Minn. Pharmacist* 27(7): 8 (1973).

M.C. Meyer, A.B. Straughn, L.J. Leeson, R.H. Levy and R.J. Sawchuk, "Meprobamate Bioavailability Monograph." *JAPhA* NS17, 173 (1977).

R.J. Sawchuk and T.S. Rector, "Burn-Induced Alterations in Drug Absorption and Disposition." *Minn. Pharmacist* 35: 6-9 (1981).

SCIENTIFIC PUBLICATIONS (NON-REFEREED)

I.E. Leppik, J. Cloyd and R.J. Sawchuk, "Coefficient of Variation as a Measure of Compliance" Letter. *Lancet*, October 14, 1978.

SCIENTIFIC PUBLICATIONS (REFEREED)

1. R.J. Sawchuk, J.M. Anderson and J.G. Nairn. "Stirring apparatus for the investigation of unstable strongly adsorbing chemicals." *J. Pharm. Sci.* 55: 1463 (1966).

2. R.J. Sawchuk and J.G. Nairn. "Rate studies on the binding of bilirubin by ion-exchange resins." *J. Pharm. Sci.* 57: 1896 (1968).

3. R.J. Sawchuk, J. Robayo and K.W. Miller. "The distribution of propranolol between blood and plasma in hypertensive patients." *Br. J. Clin. Pharmacol.* 1: 440 (1974).

4. R.J. Sawchuk and D.E. Zaske. "Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients." *J. Pharmacokin. Biopharm.* 4: 183 (1976).

5. D.E. Zaske, R.J. Sawchuk, D.N. Gerding and R.G. Strate. "Increased dosage requirements of gentamicin in burn patients." *J. Trauma* 16: (1976).

6. R.J. Sawchuk, D.E. Zaske, R.J. Cipolle, W.A. Wargin and R.G. Strate. "Kinetic model for gentamicin dosing with the use of individual patient parameters." *Clin. Pharmacol. Therap.* 21: 362 (1977).

7. J.C. Cloyd, D.E. Bosch and R.J. Sawchuk. "Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids." *Am. J. Hosp. Pharm.* 35: 45-48 (1978).

8. J.D. Wirtschafter, C.R. Volk and R.J. Sawchuk. "Trans-aqueous diffusion of acetylcholine to denervated iris sphincter muscle: A hypothetical mechanism for the tonic pupil syndrome (Adie's Syndrome). *Annals of Neurology* 4: 1-5 (1978).

9. D.E. Zaske, R.J. Sawchuk and R.G. Strate. "The necessity of increased doses of amikacin in burn patients." *Surgery* 84: 603-608 (1978).

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24. J.D. Wirtschafter, C.R. Volk and R.J. Sawchuk. "Trans-aqueous diffusion of acetylcholine to denervated iris sphincter muscle: a hypothetical mechanism for the tonic pupil syndrome (Adie's Syndrome)." Association of Research in Vision and Ophthalmology, Sarasota, FL, May 1978.

25. W.A. Wargin, M.L. Rylander, R.J. Sawchuk and J.W. McBride. "The pharmacokinetics of orally administered propranolol in hypertensive patients." APhA Academy of Pharmaceutical Sciences, Phoenix, AZ, 1977.

26. R.J. Sawchuk, J.C. Cloyd, I.E. Leppik, S.M. Pepin and R.J. Gumnit. "Steady-state analysis of phenytoin kinetics applied to dose adjustments in epileptic patients." APhA Academy of Pharmaceutical Sciences, Phoenix, AZ, 1977.

27. R.J. Cipolle, R.G. Strate, D.E. Zaske and R.J. Sawchuk. "Amikacin pharmacokinetics: effect of age on elimination." Inter-Science Conference on Antimicrobial Agents and Chemotherapy, New York, 1977.

28. D.E. Zaske, K.B. Crossley, R.J. Sawchuk, D.L. Uden and K.E. Mead. "Vancomycin kinetics: excessive steady-state serum levels resulting from recommended dosages." Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1977.

29. D.E. Zaske, R.J. Sawchuk and R.G. Strate. "Increased dosage requirements of amikacin in burn patients." American Burn Assoc., 9th Annual Meeting, Anaheim, CA, April 1977.

30. S.E. Chen, R.J. Sawchuk and E.J. Staba. "Pharmacokinetics of ginseng compounds." 2nd International Ginseng Symposium, Seoul, Korea, 1978.

31. J.C. Cloyd, R.J. Sawchuk, I.E. Leppik and S.M. Pepin. "The direct linear plot: use in estimating Michaelis-Menten parameters and individualizing phenytoin dosage regimens in epileptic patients." Epilepsy International Symposium, Vancouver, Canada, September 10-14, 1978.

32. I.E. Leppik, V. Ramani, R.J. Sawchuk and R.J. Gumnit. "Seizures and altered phenytoin metabolism in mononucleosis." Epilepsy International Symposium, Vancouver, Canada, September 10-14, 1978.

33. I.E. Leppik, J. Cloyd, R. Sawchuk and D. Fryd. "Coefficient of variation as an objective measure of compliance." Epilepsy International Symposium, Vancouver, Canada, September 10-14, 1978.

34. E. Ramsay, I. Leppik, R. Strauss, B.J. Wilder and R.J. Sawchuk. "Plasma clearance and volume of distribution of phenytoin during pregnancy." Epilepsy International Symposium, Vancouver, Canada, September 10-14, 1978.

35. R.L. Kriel, J.C. Cloyd , K.H. Green, R.J. Sawchuk, L.A. Lockman and R.M. Eggerth. "The pharmacokinetics of valproic acid in children." Child Neurology Society, Hanover, NH, September 1979.

36. P. Subronto, C.M. Stowe and R. Sawchuk. "Pharmacokinetics of aminophylline in dairy cattle." Sixtieth Conference of Research Workers in Animal Diseases, Chicago, IL, November 26-27, 1979.

37. I.E. Leppik, J. Shope, R.J. Sawchuk, W.A. Hauser and B. Van Dyne. "Variability of antiepileptic drug levels during chronic therapy." American Academy of Neurology, New Orleans, April 28-May 3, 1980.

38. R.M. Eggerth, J.C. Cloyd, R.L. Kriel and R.J. Sawchuk. "Valproic acid pharmacokinetics in epileptic children." 12th Annual Graduate Student Pharmaceutics Research Meeting, Columbus, OH, June 25, 1980.

39. R. Sylvester, R.J. Sawchuk and R. Perri. "Decreased phenytoin absorption with cis-platinum, vinblastine and bleomycin therapy." American Society of Clinical Oncology Abstracts, 1981.

40. I.E. Leppik, J. Fischer, R. Kriel and R.J. Sawchuk. "Altered phenytoin clearance during febrile illness." American Academy of Neurology, Toronto, Ontario, April 1981.

41. W.M. Awni and R.J. Sawchuk. "Preliminary pharmacokinetic studies of cyclosporin A in animals." Fourteenth Annual Graduate Student Pharmaceutics Research Meeting, Morgantown, WV, June 1982.

42. R.M. Ferguson, R. Fidelus-Gort, J.J. Rynasiewicz, K. Gajl-Peczalska, and R.J. Sawchuk. "The immunosuppressive action of cyclosporin A (CSA) in man." Annual Meeting of the American Society of Transplant Surgery, London, August 1982.

43. J.H. Fischer, I.E. Leppik, R.L. Kriel, J.D. MacDonald and R.J. Sawchuk. "Clinical significance of absorption differences between carbamazepine tablet and suspension formulations." Fourteenth Epilepsy International Symposium, London, August 1982.

44. L.E. Riad and R.J. Sawchuk. "The pharmacokinetics of carbamazepine in the rabbit." The Second University of Minnesota/3M Research Poster Session, Minneapolis, MN, May 1984.

45. W.M. Awni and R.J. Sawchuk. "Cyclosporine pharmacokinetics in the rabbit." The Second University of Minnesota/3M Research Poster Session, Minneapolis, MN, May 1984.

46. W.F. Elmquist, D.K. Yu and R.J. Sawchuk. "Propylene glycol pharmacokinetics." The Second University of Minnesota/3M Research Poster Session, Minneapolis, MN, May 1984.

47. C. Fletcher, R. Sawchuk, B. Chinnock, C. Vicary, L.E. Kirk, P. De Miranda, and H.H. Balfour, Jr. "Human pharmacokinetics of 9-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine." Interscience Conference on Antimicrobial Agents and Chemotherapy, Minneapolis, MN, September 28, 1985.

48. R.J. Sawchuk, L. Riad and K.K.H. Chan. "Simultaneous first- and zero-order absorption of carbamazepine (Tegretol) tablets in humans." 16th Epilepsy International Congress, Hamburg, West Germany, September 6, 1985.

49. W.M. Awni and R.J. Sawchuk. "Differential absorption of cyclosporine from two consecutive anatomic regions of the small intestine using an *in situ* perfusion model." Academy of Pharmaceutical Sciences Meeting, Minneapolis, MN, October 20, 1985.

50. H.A. Abou-Auda and R.J. Sawchuk. "Absorption and metabolism of salicylate esters in rabbit small intestine." Academy of Pharmaceutical Sciences Meeting, Minneapolis, MN, October 18-24, 1985.

51. L.E. Riad, K.K.H. Chan and R.J. Sawchuk. "Contribution of epoxide pathway to induction of carbamazepine metabolism during multiple dosing in humans." Academy of Pharmaceutical Sciences meeting, Minneapolis, MN, October 18-24, 1985.

52. L.E. Riad and R.J. Sawchuk. "Contribution of epoxide formation to the auto-induction of carbamazepine in the rabbit." Academy of Pharmaceutical Sciences Meeting, Minneapolis, MN, October 18-24, 1985.

53. R.M. Eggerth and R.J. Sawchuk. "Investigation of the dose-dependent elimination of phenytoin in the rabbit." Academy of Pharmaceutical Sciences Meeting, Minneapolis, MN, October 18-24, 1985.

54. L.E. Riad and R.J. Sawchuk. "Determination of the relative formation of elimination clearance of carbamazepine metabolites in humans: a comparison of traditional and pooled sample analysis." Third European Congress of Biopharmaceutics and Pharmacokinetics, Freiburg, Germany, April 21, 1987.

55. W.F. Elmquist, D.K. Yu, G. Solis and R.J. Sawchuk. "Physiological modelling of the dependence of renal clearance on urine flow: propylene glycol pharmacokinetics in man." Third European Congress of Biopharmaceutics and Pharmacokinetics, Freiburg, Germany, April 21, 1987.

56. A.K. Shah, K.D. Lake and R.J. Sawchuk. "Blood levels of cyclosporine A and its metabolites in rabbit and man." American Association of Pharmaceutical Scientists Annual Meeting, Boston, MA, June 1987.

57. K.D. Lake, Pharm.D.*, A.K. Shah, Ph.D., R. Emery, M.D. and R.J. Sawchuk, Ph.D. "Measurement of cyclosporine metabolites in the blood of heart transplant recipients." American College of Clinical Pharmacy Annual Meeting, May 1987.

58. A.K. Shah, A. Gratwohl and R.J. Sawchuk. "Subcutaneous absorption of cyclosporine in rabbits." 2nd International Congress on Cyclosporine, Washington, DC, November 4-7, 1987.

59. M.A. Hedaya and R.J. Sawchuk. "The effect of probenecid on the renal excretion of azidothymidine (AZT) in the rabbit." Third Annual Meeting, AAPS, Orlando, FL, October 29-November 4, 1988.

60. W.F. Elmquist, K.K.H. Chan, V.A. John and R.J. Sawchuk. "Transsynovial distribution of diclofenac. " Third Annual Meeting, AAPS, Orlando, FL, October 29-November 4, 1988.

61. L.E. Riad and R.J. Sawchuk. "Administration of site-related differences in carbamazepine disposition in the rabbit." Third Annual Meeting, AAPS, Orlando, FL, October 29-November 4, 1988.

62. A.K. Shah and R.J. Sawchuk. "Effect of urine flow on the renal clearance of cyclosporine in rabbit." Third Annual Meeting, AAPS, Orlando, FL, October 29-November 4, 1988.

63. W.F. Elmquist, L.E. Riad, I.E. Leppik and R.J. Sawchuk. "Physiological modelling of the dependence of renal clearance on urine flow: carbamazepine and two metabolites in man." Third Annual Meeting, AAPS, Orlando, FL, October 29-November 4, 1988.

64. M.A. Hedaya and R.J. Sawchuk. "Pharmacokinetic analysis of the enhanced distribution of zidovudine into rabbit cerebrospinal fluid caused by probenecid." V. International Conference on AIDS, Montreal, June 4-9, 1989.

65. Y. Wang, M.A. Hedaya and R.J. Sawchuk. "Effect of mannitol IV infusion on distribution of zidovudine between plasma and cerebrospinal fluid in rabbits." V. International Conference on AIDS, Montreal, June 4-9, 1989.

66. M.A. Hedaya, W.F. Elmquist and R.J. Sawchuk. University of Minnesota, Minneapolis, Minnesota, USA. "Probenecid inhibits the metabolic and renal clearances of zidovudine in human volunteers." V. International Conference on AIDS, Montreal, June 4-9, 1989.

67. M.A. Hedaya and R.J. Sawchuk. "A sensitive and specific HPLC method for the determination of zidovudine and zidovudine glucuronide in plasma and urine." V. International Conference on AIDS, Montreal, June 4-9, 1989.

68. M.A. Hedaya and R.J. Sawchuk. "A simple and specific liquid-chromatographic method for determination of ganciclovir (DHPG) in plasma and urine." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

69. L.E. Riad and R.J. Sawchuk. "Intestinal absorption of carbamazepine in the rabbit." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

70. A.J. Shah and R.J. Sawchuk. "The effect of altering blood lipids on the pharmacokinetics of cyclosporine in the rabbit." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

71. M.A. Hedaya, W.F. Elmquist and R.J. Sawchuk. "Mechanism of zidovudine (AZT) dose-sparing by probenecid in humans." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

72. W.F. Elmquist and R.J. Sawchuk. "Tissue mean transit time determination from steady-state partition coefficients and tissue/plasma concentration ratios in the post-distributive phase." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

73. L.E. Riad and R.J. Sawchuk. "Relative bioavailability and effects of food on plasma levels of diclofenac sodium following a single oral dose of Voltaren 100-mg SR tablet." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

74. O.H. Chan and R.J. Sawchuk. "Intestinal absorption of diltiazem in the rabbit." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

75. R.J. Sawchuk. "Pharmacokinetic and analytical considerations in monitoring zidovudine (AZT) levels in children with AIDS." The Fourth International Congress on Pediatric Laboratory Medicine, Washington, DC, August 23, 1989.

76. K.D. Lake, A.K. Shah, R.W. Emery, D.R. Holder and R.J. Sawchuk. "The effect of urine flow rate on the renal clearance of cyclosporine in heart transplant recipients." International Society for Heart Transplantation, Tenth Annual Meeting, Fort Lauderdale, FL, April 4-6, 1990.

77. R.J. Sawchuk. "Effect of temperature and medium of analysis on CsA concentration." Canadian Consensus Meeting on Cyclosporine Monitoring, Minaki Lodge, Ontario, May 10-13, 1990.

78. H. Das, S.W. Wong, K. Chan, R.J. Sawchuk and R.L. Oberle. "Pharmacokinetics and metabolism of diclofenac sodium (Voltaren) after IV and oral administration to Yucatan miniswine." Eastern Regional AAPS meeting, New Brunswick, NJ, June 3-5, 1990.

79. S.M. Wong and R.J. Sawchuk. "Interaction of zidovudine and probenecid at steady state." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics." Erice, Sicily, September 4-15, 1990.

80. W.F. Elmquist and R.J. Sawchuk. "Tissue mean transit time determination from steady-state partition coefficients and tissue/plasma concentration ratios in the postdistributive phase." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics," Erice, Sicily, September 4-15, 1990.

81. A.K. Shah, R.J. Sawchuk, A. Gratwohl and R.C. Brundage. "Modeling subcutaneous absorption of cyclosporine A in rabbits." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics," Erice, Sicily, September 4-15, 1990.

82. L.E. Riad, K.K.H. Chan and R.J. Sawchuk. "Effects of dosing rate on carbamazepine enzymatic induction in normal volunteers." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics," Erice, Sicily, September 4-15, 1990.

83. W.F. Elmquist, L.E. Riad, I.E. Leppik and R.J. Sawchuk. "The relationship between carbamazepine urine and plasma concentrations: implications for therapeutic drug monitoring." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

84. S.M. Wong, L.E. Riad, P. Degen, V. John, K. Chan and R.J. Sawchuk. "Comparison of plasma concentrations of diclofenac sodium and its metabolites during single and multiple dosing of Voltaren SR tablet in humans." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

85. O.H. Chan and R.J. Sawchuk. "Saturable first-pass elimination of diltiazem during intestinal absorption in the rabbit." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

86. L.E. Riad and R.J. Sawchuk. "Carbamazepine enzymatic induction: extent and effects of dosing rate in normal volunteers." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

87. Y.-F. Wang, M.A. Hedaya and R.J. Sawchuk. "Comparative absorption and disposition pharmacokinetics of AZT and AZddU in rabbits." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

88. S.L. Wong and R.J. Sawchuk. "Investigation of distribution of zidovudine into the brain by microdialysis." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

89. S.L. Wong and R.J. Sawchuk. "Interaction of zidovudine and probenecid at steady state." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

90. S.L. Wong, Y.-F. Wang and R.J. Sawchuk. "Brain/plasma distribution kinetics of zidovudine (AZT) in the rabbit using microdialysis." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN, May 16-17, 1991.

91. K. Van Belle, S.L. Wong, Y.-F. Wang and R.J. Sawchuk. "Comparative delivery and distribution kinetics of zidovudine (AZT) and AZddU into the rabbit brain by microdialysis." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN, May 16-17, 1991.

92. Y.-F. Wang, S.L. Wong and R.J. Sawchuk "*In vitro* and *in vivo* calibration of microdialysis probes using retrodialysis." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN, May 16-17, 1991.

93. B.W. Cheung, L.E. Riad and R.J. Sawchuk. "Comparative uptake of selected anticonvulsant drugs into rabbit brain." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN May 16-17, 1991.

94. L.E. Riad, K.K. Chan, J.A. Maloney and R.J. Sawchuk. "Reversibility of carbamazepine autoinduction upon dose termination in normal volunteers." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

95. S.L. Wong, M.A. Hedaya and R.J. Sawchuk. "Modeling the competitive inhibition of renal and nonrenal clearance of zidovudine by probenecid." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

96. K. Van Belle, S.L. Wong, Y.-F. Wang and R.J. Sawchuk. "Comparison of pharmacokinetics and CNS distribution of coadministered AZT and AZddU by microdialysis." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

97. Y.-F. Wang, S.L. Wong and R.J. Sawchuk. "*In vitro* and *in vivo* calibration of microdialysis probes using retrodialysis: application to the study of brain/plasma distribution of zidovudine." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

98. W.F. Elmquist, L.E. Riad, I.E. Leppik and R.J. Sawchuk. "The relationship between urine and plasma concentrations of carbamazepine and phenytoin in epileptic patients on chronic therapy." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

99. S.L. Wong, Y.-F. Wang, and R.J. Sawchuk. "Effect of dose on distribution of zidovudine (AZT) into rabbit brain using microdialysis with *in vivo* calibration." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

100. W.F. Elmquist, I.E. Leppik and R.J. Sawchuk. "Physiological modeling of the dependence of renal clearance on urine flow II: phenytoin and HPPH in humans." American Association of Pharmaceutical Scientists Annual Meeting, Washington, DC, November 17-21, 1991.

101. R.J. Sawchuk. "Study of zidovudine distribution into the CNS utilizing microdialysis." 25th Annual Higuchi Research Seminar, Lake of the Ozarks, MO, March 8-11, 1992.

102. Y.F. Wang and R.J. Sawchuk. "Microdialysis studies of brain/plasma distribution of AZT during intraventricular and intravenous infusion." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

103. S.L. Wong, K. Van Belle, and R.J. Sawchuk. "A microdialysis study of probenecid's effect on the transport kinetics of zidovudine in rabbit brain." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

104. S.L. Wong, and R.J. Sawchuk. "Pharmacokinetic interaction of zidovudine and salicylic acid during continuous infusion." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

105. S.L. Wong, and R.J. Sawchuk. "Effect of salicylic acid on the distribution of zidovudine between plasma and cerebrospinal fluid." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

106. R.C. Brundage, K.K.H. Chan, and R.J. Sawchuk. "Population pharmacokinetic modeling of nicotine following transdermal drug administration." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

107. R.C. Brundage, K.K.H. Chan, and R.J. Sawchuk. "Population pharmacokinetics of diclofenac potassium using routinely collected experimental data." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

108. W.F. Elmquist and R.J. Sawchuk. "Simulation of the effect that the time delay in sampling from the bladder has on urine concentrations: implications for therapeutic drug monitoring using urine specimens." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

109. J.P. Zhong, Y.F. Wang and R.J. Sawchuk. "Absorption of three antiviral nucleosides from different anatomic regions of rabbit intestine." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

110. Y.F. Wang, S.L. Wong, and R.J. Sawchuk. "On-line microdialysis calibration using retrodialysis and the zero-net flux method: application to a study of the distribution of AZT to rabbit CSF and thalamus." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

111. R.J. Sawchuk. "Comparative distribution of AZT into brain tissue extracellular fluid during intravenous and intraventricular infusion using microdialysis." 26th Annual Higuchi Research Seminar, Lake of the Ozarks, MO, March 14-17, 1993.

112. Y. Wang and R.J. Sawchuk, "Comparison of renal clearance of AZdU following IV bolus and constant-rate Infusion." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

113. Y. Wang and R.J. Sawchuk. "Assessment of oral absorption of AZT and AZdU in the rabbit using deconvolution." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

114. Y. Wang, Y. Wei and R.J. Sawchuk. "Microdialysis studies of carrier-mediated transport of AZT from brain to plasma during intracerebroventricular infusion." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

115. B.K. Malhotra, M. Lemaire, and R.J. Sawchuk. "Investigation of the CNS distribution of EAB 515 in freely moving rats by microdialysis." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

116. A.K. Shah, R.C. Brundage, K.D. Lake and R.J. Sawchuk. "Estimation of plasma free fraction (fu) of cyclosporine (CYA) in the rabbit and heart transplant (HT) patients by NONMEM using a physiological model of renal clearance (CLr)." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

117. B.K. Malhotra, R.C. Brundage, M. Lemaire, and R.J. Sawchuk. "Modeling of the CNS distribution of EAB 515 following IV and ICV administration." 5th Symposium: Frontiers of Pharmacokinetics and Pharmacodynamics, Baltimore, MD, April 18-20, 1994.

118. R.C. Brundage, B.K. Malhotra, J.A. Maloney and R.J. Sawchuk. "Brain distribution of tacrine and the 1-hydroxy and 2-hydroxy tacrine metabolites determined by microdialysis in freely-moving rats." 5th Symposium: Frontiers of Pharmacokinetics and Pharmacodynamics, Baltimore, MD, April 18-20, 1994.

119. Y. Wang and R.J. Sawchuk. "CNS Distribution of inulin-[^{14}C]-carboxylic acid in rabbits." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

120. B.K. Malhotra, R.C. Brundage and R.J. Sawchuk. "Simultaneous microdialysis of portal and jugular blood following IV bolus and oral lavage in freely-moving rats." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

121. R.C. Brundage, B.K. Malhotra, J.A. Maloney and R.J. Sawchuk. "Brain distribution of tacrine and its 1- and 2-hydroxylated metabolites determined by microdialysis in freely-moving rats." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

122. B.K. Malhotra, R.C. Brundage, Y. Wang and R.J. Sawchuk. "Dialysis membrane-limited and aqueous boundary layer-limited *in vitro* microdialysis recovery." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

123. B.W.Y. Cheung, Y. Wang and R.J. Sawchuk. "Preliminary studies of effects of hydroxy-propyl-beta-cyclodextrin on carbamazepine distribution into rabbit brain." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

124. R.J. Sawchuk, J.A. Maloney, L.L. Cartier, R.J. Rackley, K.K.H. Chan and H.S.H. Lau. "Analysis of diclofenac and four of its metabolites in human urine by HPLC." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

125. R.C. Brundage, M. Lemaire and R.J. Sawchuk. "Modeling of the CNS distribution of EAB 515 following IV and ICV administration." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

126. B.K. Malhotra, M. Lemaire, J.F. Brouillard and R.J. Sawchuk. "High-performance liquid chromatographic (HPLC) analysis of EAB 515 in brain and blood microdialysate (on-line) and in plasma ultrafiltrate of freely-moving rats." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

127. R.J. Sawchuk, R.C. Brundage, E.D. Kharasch and M.D. Karol. "Physiological-based pharmacokinetic (PBPK) modeling of sevoflurane, a volatile anesthetic." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

128. R.C. Brundage, S. Thomas Forgue and R.J. Sawchuk. "Comparative distribution of a series of aminoacridines of varying polarities into rat cortex using microdialysis." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

129. Z. Yang, R.C. Brundage, L.L. Cartier, J.A. Maloney and R.J. Sawchuk. "Development of a microdialysis method to study brain distribution of stavudine (d4t) in freely-moving rats." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

130. B.K. Malhotra, R.C. Brundage and R.J. Sawchuk. "Estimation of presystemic disposition of drugs based upon combination of area ratios and deconvolution." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

131. M.A. Osman, R. J. Sawchuk, and M.K. Youssef. "In Situ Absorption of the Antiviral drug, stavudine, from the rabbit intestine." European Symposium on Formulation of Poorly Available Drugs for Oral Administration, Paris, February 5- 6, 1996.

132. M.A. Osman, R.J. Sawchuk, and M.K. Youssef. "Ganciclovir (DHPG), an antiviral nucleoside that exhibits high absorptive clearance in the rabbit colon *in situ*." European Symposium on Formulation of Poorly-available Drugs for Oral Administration, Paris, February 5- 6, 1996.

133. B. K. Malhotra, M. Lemaire, J.F. Brouillard, and R.J. Sawchuk. "High-performance liquid chromatographic (HPLC) analysis of EAB 515 in brain and blood microdialysate (on-line) and in plasma ultrafiltrate of freely-moving rats." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, October 29-31, 1996.

134. R.J. Sawchuk, R.C. Brundage, E.D. Kharasch, and M.D. Karol. "Physiologically-based pharmacokinetic (PBPK) modeling of sevoflurane, a volatile anesthetic." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, October 29-31, 1996.

135. R.C. Brundage, S.T. Forgue, and R.J. Sawchuk. "Comparative distribution of a series of aminoacridines of varying polarities into rat cortex using microdialysis." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, October 29-31, 1996.

136. Z. Yang, R.C. Brundage, L.L. Cartier, J.A. Maloney, and R.J. Sawchuk. "Development of a microdialysis method to study brain distribution of stavudine (d4T) in freely-moving rats." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, October 29-31, 1996.

137. B.K. Malhotra, R. C. Brundage, and R. J. Sawchuk. "Estimation of presystemic disposition of drugs based upon combination of area ratios and deconvolution." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, October 29-31, 1996.

138. Z. Yang and R.J. Sawchuk. "A modified solvent drag model and its application in studying intestinal absorption of polar drugs." 12th Annual Meeting, American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

139. Z. Yang and R.J. Sawchuk. "Estimating the intestinal absorptive clearance of drugs: consideration of water absorption during in situ single-pass perfusion studies." 12th Annual Meeting, American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

140. Z. Yang, P. Manitpisitkul, F.P. LaCreta, C.K. Knupp, R.H. Barbhaiya, and R.J. Sawchuk. "*In situ* studies of the regional absorption of lobucavir and ganciclovir from rabbit intestine." American Association of Pharmaceutical Scientists Annual Meeting, San Francisco, CA, November 15-19, 1998.

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147. B.W.Y. Cheung, L.L. Cartier, H. Q. Russlie, and R.J. Sawchuk. "Using Sample Pooling Methods in the Determination of AUC and AUMC in Pharmacokinetic Studies" *American Association of Pharmaceutical Scientists Annual Meeting*, New Orleans, LA, November 14-18, 1999.

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153. J.Z. Peng, R.C. Brundage, and R.J. Sawchuk. "Study of Presystemic Elimination of 4-mono-methylamino-antipyrine (MAAP) after Consecutive Doses in Freely Moving Rats Using On-line Microdialysis". *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

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155. G. Gan, L. L. Cartier, Y. Huang, Z. Yang, R. J. Sawchuk "Intestinal Absorption and Presystemic Elimination of the Prokinetic Agent, EM574, in Rabbits" *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

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157. Z. Yang, L. M. Zadjura, C. J. D'Arienzo, D. B. Wang-Iverson, R. J. Sawchuk "Use of Sample Pooling in Drug Discovery to Screen for Pharmacokinetic Properties of Compounds in Rats" *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

158. R.J. Sawchuk, Y. Huang, P. Ji, M. Quartey, G.S. Giebink. "Influx/Eflux Penetration Clearance of Amoxicillin between Plasma and Middle Ear Fluid in Freely Moving Chinchillas using Microdialysis" *4th Extraordinary International Symposium on Recent Advances in Otitis Media*, Sendai, Japan, April 16-20, 2001.

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160. W. Liu, B.W. Cheung, L.L. Cartier, T. Zhu, M.M. Paris, R.J. Sawchuk. "In vitro/In vivo Microdialysis and Protein Binding Studies of the ketolide antibiotic, ABT-773." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

161. Y. Huang, R.J. Sawchuk. "Estimation of Amoxicillin Influx and Efflux Clearance between Plasma and Middle Ear Fluid Following Simultaneous Systemic and Local Ear Doses in Awake Chinchilla Using Microdialysis." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

162. J.Z. Peng, R.C. Brundage, R.J. Sawchuk. "The Influence of Drug Pre-exposure on First-pass Metabolism of Tacrine in Rats." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

163. J Peng, R J Sawchuk, and R P Remmel "Mechanism-based inactivation of CYP1A2 by tacrine" *11th North American Meeting of the International Society for the Study of Xenobiotics*, Orlando, FL. October 27-31, 2002.

164. Y Song, L L Cartier, B W Cheung, R J Sawchuk. "An Animal Model for Multi-site CSF Disposition Studies of Intrathecally Administered Agents". *American Association of Pharmaceutical Scientists Annual Meeting*, Toronto, Ontario, Canada. November 10-14, 2002.

165. J Z Peng, R Remmel, R J Sawchuk. "Modeling And Simulation Of In Vivo PK Profiles Based On Mechanism-based Inhibition From In Vitro Studies: Inactivation Of CYP1A2 by Tacrine" *American Association of Pharmaceutical Scientists Annual Meeting*, Toronto, Ontario, Canada. November 10-14, 2002.

166. Y Song, L L Cartier, BW Cheung, R J Sawchuk. "Multi-site CSF Disposition Studies of Intrathecally Administered Antiviral Nucleosides in a Novel Animal Model". *8th International Meeting of the International Society for the Study of Xenobiotics*, Dijon France. April 27-31, 2003

167. W Liu, B W Y. Cheung, R J Sawchuk. "Distribution Kinetics of Cethromycin in the Chinchilla Middle Ear". *8th International Symposium on Recent Advances in Otitis Media*. Fort Lauderdale, FL. June 3 - 7, 2003

168. P Ji, L Cartier, B W Y Cheung, R J Sawchuk. "Distribution Kinetics Of Cefdinir Between Plasma And Middle Ear Fluid In The Freely Moving Chinchillas". *American Association of Pharmaceutical Scientists Annual Meeting*, Salt Lake City, UT. October 26-30, 2003.

169. W Liu, B W Y Cheung, R J Sawchuk. "Efflux Transport Of Cethromycin Following Direct Intra-bulla Dosing In The Chinchilla Middle Ear". *American Association of Pharmaceutical Scientists Annual Meeting*, Salt Lake City, UT. October 26-30, 2003.

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171. N Mostafa and R J Sawchuk. "Determination of Ofloxacin Clearance from the Middle Ear Fluid using Microdialysis". *American Association of Pharmaceutical Scientists Annual Meeting*, Nashville, TN. November 7, 2005.

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EXHIBIT 21

RANDOM HOUSE WEBSTER'S COLLEGE DICTIONARY

RANDOM HOUSE
NEW YORK

The first Random House college dictionary, the *American College Dictionary*, was published in 1947 to critical acclaim. The first edition of the *Random House Webster's College Dictionary* was published in 1991. Subsequent revisions were published in 1992, 1995, and 1996. A second, completely redesigned, revised, and updated edition was published in 1997, with updates published annually thereafter.

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liturgy (lit′ər jē) *n.* [1325–75; ME *liturgie* < ML *liturgia* (< LGk) < LL *lethargia* < Gk *leitourgía* = *leitourg(ós)* drowsy (akin to *léthē*, see LETHE) + *-ia* -IA] —**lit′ur·gist**, *n.*

Leth·bridge (leth′brij′), *n.* a city in S Alberta, in SW Canada. 58,641.

Le·the (lē′thē), *n.* **1.** a river in the ancient Greek underworld whose water caused those who drank it to forget their past. **2.** (*usu. l.c.*) forgetfulness; oblivion. [< L < Gk *léthē* lit., forgetfulness; der. of *lanthánein* to forget] —**Le·the′an** (lē thē′ən, lē′thē ən), *adj.*

let′s (lets), contraction of *let us.* —**Usage.** See CONTRACTION, LET².

Let (let), *n.* Latvian (def. 1).

let·ted (let′id), *v.* a pt. and pp. of LET².

let·ter (let′ər), *n.* **1.** a written or printed communication addressed to a person or organization and usu. transmitted by mail. **2.** a symbol or character that is conventionally used in writing and printing to represent a speech sound and is part of an alphabet. **3.** a piece of printing type bearing such a symbol or character. **4.** a particular style of type. **5.** Often, **letters.** a formal document granting a right or privilege. **6.** actual terms or wording; literal meaning, as distinct from implied meaning or intent (opposed to *spirit*): *the letter of the law.* **7. letters,** (used with a sing. or pl. v.) **a.** literature in general. **b.** the profession of literature. **c.** learning; knowledge, esp. of literature. **8.** an emblem consisting of the initial or monogram of a school, awarded to a student for accomplishment, esp. in athletics. —*v.t.* **9.** to mark or write with letters; inscribe. —*v.i.* **10.** to earn a letter in a school activity, esp. a sport. —*Idiom.* **11. to the letter,** to the last particular; precisely. [1175–1225; ME, var. of *lettre* < OF < L *littera* alphabetic character, pl. epistle, literature] —**let′ter·er**, *n.*

let′ter bomb′, *n.* an envelope containing an explosive device designed to detonate when the envelope is opened. [1945–50]

let′ter box′, *n.* a public or private mailbox. [1765–75]

let′ter car′rier, *n.* MAIL CARRIER. [1545–55]

let·tered (let′ərd), *adj.* **1.** educated or learned. **2.** literate. **3.** of or characterized by learning or literary culture. **4.** marked with or as if with letters. [1275–1325]

let·ter·form (let′ər fôrm′), *n.* the shape of a letter of the alphabet with regard to its design or historical development. [1905–10]

let′ter·head (let′ər hed′), *n.* **1.** a printed heading on stationery, esp. one giving the name and address of a person, business concern, institution, etc. **2.** a sheet of paper with such a heading. [1885–90]

let·ter·ing (let′ər ing), *n.* **1.** the act or process of inscribing with or forming letters. **2.** the letters inscribed. [1635–45]

let′ter of cred′it, *n.* **1.** a document issued by a banker allowing the person named to draw money to a specified amount. **2.** a letter from a bank notifying a person that drafts on the issuer have been authorized up to a specified amount. [1635–45]

let′ter (or **let′ters**) **of mar′que**, *n.* license granted by a state to a private citizen to capture and confiscate the merchant ships of another nation. Also called **let′ter of mar′que and repris′al.** [1400–50]

let′ter-per′fect, *adj.* **1.** knowing one's part, lesson, or the like, perfectly. **2.** precise or exact in every detail. [1880–85]

let′ter·press, (let′ər pres′), *n.* **1.** the process of printing from letters or type in relief. **2.** matter printed in such a manner. —*adj.* **3.** set in letterpress: *letterpress work.* [1750–60]

let′ter-qual′i·ty, *adj.* designating or producing type equal in sharpness and resolution to that produced by an electric typewriter: *a letter-quality computer printer.* Abbr.: LQ. [1975–80]

let′ter-size′, *adj.* **1.** (of paper) measuring approximately 8½ × 11 in. (22 × 28 cm). **2.** (of office supplies and equipment) made for holding letter-size sheets of paper. Compare LEGAL-SIZE.

let′ters of administra′tion, *n.pl.* an instrument issued by a court or public official authorizing an administrator to take control of and dispose of the estate of a deceased person. [1490–1500]

let′ters (or **let′ter**) **of cre′dence**, *n.pl.* (or *n.*) credentials issued to a diplomatic representative for presentation to a foreign country. Also called **let′ters creden′tial.**

let′ters pat′ent, *n.pl.* an instrument issued by a government conferring a right upon a patentee, esp. an exclusive right to make and sell an invention. [1350–1400]

let′ters testamen′tary, *n.pl.* an instrument issued by a court or public official authorizing an executor to take control of and dispose of the estate of a deceased person.

Let·tish (let′ish), *adj.* **1.** of or pertaining to the Latvians or their language. —*n.* **2.** LATVIAN (def. 2). [1825–35]

let·tre de ca·chet (le trə′ də ka shā′), *n., pl.* **let·tres de ca·chet** (le trə′ də ka shā′). *French.* a letter under the seal of the sovereign, esp. one ordering imprisonment, frequently without trial.

let·tuce (let′is), *n.* **1.** a cultivated composite plant, *Lactuca sativa*, occurring in many varieties and having succulent leaves used for salads. **2.** the leaves of this plant. **3.** *Slang.* paper money; cash. [1250–1300; ME *letuse*, appar. < OF *laitues*, pl. of *laitue* < L *lactūca* a lettuce]

let·up (let′up′), *n.* cessation; pause; relief. [1835–45, *Amer.*]

le·u (le′o͞o), *n., pl.* **lei** (lā). the basic monetary unit of Romania. [1875–80; < Romanian; lit., LION]

Leu, leucine.

leu·cine (lo͞o′sēn, -sin), *n.* one of the essential amino acids, $(CH_3)_2CHCH_2CH(NH_2)COOH$, present in most proteins. *Abbr.:* Leu; *Symbol:* L. [< *F* (1820) < Gk *leuk(ós)* white + *F -ine* -INE²]

leu·cite (lo͞o′sīt), *n.* a feldspathoid mineral, potassium aluminum silicate, $KAlSi_2O_6$, found in potassium-rich igneous rocks. [< *G Leucit* (1791) < Gk *leuk(ós)* white + *G -it* -ITE¹] —**leu·cit′ic** (-sit′ik), *adj.*

leuco-, var. of LEUKO-

leu·co·plast (lo͞o′kə plast′), *n.* a starch-storing colorless plastid in the cells of roots and underground or internal plant parts. [1885–90]

leuk-, var. of LEUKO- before a vowel.

leu·ke·mi·a (lo͞o kē′mē ə), *n.* any of several cancers of the bone marrow characterized by an abnormal increase of white blood cells in the tissues. [earlier *leuchaemia* < *G Leukämie* (1848). See LEUKO-, -EMIA] —**leu·ke′mic**, *adj., n.*

leuko-, a combining form with the meanings "white," "white blood cell": *leukopoiesis, leukotomy.* Also, **leuco-** *esp. before a vowel,* **leuk-**. [< Gk comb. form of *leukós* white, bright]

leu·ko·cyte or **leu·co·cyte** (lo͞o′kə sīt′), *n.* WHITE BLOOD CELL. [1865–70] —**leu′ko·cyt′ic** (-sit′ik), *adj.*

leu·ko·cy·to·sis or **leu·co·cy·to·sis** (lo͞o′kō sī tō′sis), *n.* an increase in the number of white blood cells in the blood. [1865–70]

leu·ko·ma or **leu·co·ma** (lo͞o kō′mə), *n.* a dense, white opacity of the cornea. [1700–10; < NL *leucoma*. See LEUKO-, -OMA]

leu·ko·pe·ni·a or **leu·co·pe·ni·a** (lo͞o′kə pē′nē ə), *n.* a decrease in the number of white blood cells in the blood. [1895–1900] —**leu′ko·pe′nic**, *adj.*

leu·ko·pla·ki·a or **leu·co·pla·ki·a** (lo͞o′kə plā′kē ə), *n.* a condition marked by one or more white patches on a mucous membrane, as of the tongue or cheek, usu. benign. [1880–85; < Gk *leuko-* LEUKO- + *plak-*, s. of *pláx* flat surface, taken as "tongue" + *-ia* -IA; cf. *leukoplasia* for earlier *leucoplacia*, as if formed with -PLASIA]

leu·ko·po·e·sis or **leu·co·po·e·sis** (lo͞o′kō pō ē′sis), *n.* the formation and development of white blood cells. [1910–15] —**leu′ko·pot′ic** (-pot′ik), *adj.*

leu·ko·tri·ene or **leu·co·tri·ene** (lo͞o′kə trī′ēn), *n.* any of a group of $C_{20}H_{32}O_3$ produced by white blood cells in an immune response to antigens, that contributes to allergic asthma and inflammatory reactions. [1975–80; LEUKO- + *triene* (see TRI-, -ENE)]

Leu·ven (lo͞o′vən, lo͞o′-), *n.* a city in central Belgium. 84,100. French, **Louvain.**

lev (lef), *n., pl.* **lev·a** (lev′ə), the basic monetary unit of Bulgaria. [1900–05; < Bulgarian; lit., lion]

Lev., Leviticus.

Le·val·loi·si·an (lev′ə loi′zē ən, -zhən) also **Le·val·lois** (la val′wä), *adj.* of or designating a late Lower and Middle Paleolithic method of striking sharp-edged flake tools from a prepared stone core. [1930–35; LEVALLOIS(-PERRET) + -IAN]

Le·val·lois-Per·ret (la val wa′ pe re′), *n.* a suburb of Paris, in N France, on the Seine. 53,500.

Le·vant (li vant′), *n.* the lands bordering the E shores of the Mediterranean Sea. [1490–1500; earlier *levaunt* < MF *levant*, n. use (with reference to rising sun) of prp. of *lever* to raise (*se lever* to rise). See LEVER]

le·vant·er (li van′tər), *n.* **1.** a strong easterly wind in the Mediterranean. **2.** (*cap.*) LEVANTINE. [1620–30]

Le·van·tine (lev′ən tīn′, -tēn′, li van′tīn, -tin), *adj.* **1.** of or pertaining to the Levant. —*n.* **2.** a native or inhabitant of the Levant. [1640–50] —**Lev′an·tin′ism**, *n.*

le·va·tor (li vā′tər, -tôr), *n., pl.* **lev·a·to·res** (lev′ə tôr′ēz, -tōr′-). **1.** a muscle that raises a part of the body. Compare DEPRESSOR. **2.** a surgical instrument used to raise a depressed part of the skull. [1605–15; < NL; cf. ML *levātor* one who raises recruits < L *levāre* to raise]

lev·ee¹ (lev′ē), *n.* **1.** an embankment designed to prevent the flooding of a river. **2.** a natural deposit of sand or mud built up along the side of a river or stream. **3.** one of the small continuous ridges surrounding fields that are to be irrigated. **4.** a landing place for ships. —*v.t.* **5.** to furnish with a levee. [1710–20; < *F levée* < ML *levāta* embankment, n. use of fem. ptp. of L *levāre* to raise (see LEVER)]

lev·ee² (lev′ē, le vē′), *n.* **1.** (in Great Britain) a public court assembly, held in the early afternoon, at which men only are received. **2.** a formal reception, usu. in someone's honor: *a presidential levee; the Governor General's levee.* **3.** (formerly) a reception of visitors held on rising from bed, as by a royal personage. [1665–75; < *F levé* var. sp. of *lever* rising < L *levāre* to raise; see LEVER]

lev·el (lev′əl), *adj., n., v.,* **-eled, -el·ing** or (*esp. Brit.*) **-elled, -el·ling.** —*adj.* **1.** having no part higher than another; having a flat or even surface. **2.** being in a plane parallel to the plane of the horizon; horizontal. **3.** equal, as in height, condition, status, or advancement. **4.** even, equable, or uniform: *to speak in a level voice.* **5.** filled to a height even with the rim of a container: *a level teaspoon of salt.* **6.** mentally well-balanced; sensible; rational: *to keep a level head in a crisis.* **7.** of or pertaining to a particular rank or involving members of such a rank (usu. used in combination): *high-level discussions.* —*n.* **8.** the horizontal line or plane in which anything is situated with regard to its elevation: *a shelf built at eye level.* **9.** a position with respect to a given or specified height: *The water rose to a level of 80 feet.* **10.** a position or plane in a graded scale of values: *an average level of skill.* **11.** rank or status, as in a hierarchy: *the top levels of government.* **12.** stratum or sphere: *levels of meaning; elections on a local level.* **13.** an extent, measure, or degree of intensity, concentration, quantity, etc.: *low levels of radiation; to increase levels of production.* **14.** a horizontal surface, as a floor in a building or other structure: *the upper level of the bridge.* **15.** a device, as a spirit level, used for determining or adjusting something to a horizontal surface. **16.** a surveying instrument consisting of a spirit level mounted on a frame with a telescopic sight, used for establishing a horizontal. **b.** an observation made with this instrument. **17.** an imaginary line or surface everywhere at right angles to the plumb line. **18.** a horizontal position or condition. **19.** a level or flat surface, as an extent of land approximately horizontal and

unbroken by irregularities. 20. the interconnected horizontal mine workings at a particular elevation or depth: *the 1500-foot level.* —*v.t.* 21. to make (a surface) level, even, or flat; make horizontal. 22. to raise or lower to a particular level or position. 23. to bring (something) to the level of the ground: *to level trees.* 24. *Informal.* to knock down (a person). 25. to make equal, as in status or condition. 26. to make even or uniform, as coloring. 27. to aim or point (a weapon, criticism, etc.) at a mark or objective. 28. to find the relative elevation of different points in (land), as with a surveyor's level. —*v.i.* 29. to bring things or persons to a common level. 30. to aim a weapon, criticism, etc., at a mark or objective. 31. to speak truthfully and openly (often fol. by *with*). 32. a. to take a level in surveying. b. to use a leveling instrument. 33. **level off,** a. (of an aircraft) to maintain a constant altitude after a climb or descent. b. to become stable; reach a constant or limit. c. to make even or smooth. —*Idiom.* 34. **find one's (own) level,** to attain a position or status that matches one's ability. 35. **one's level best,** one's very best; one's utmost. 36. **on the level,** honest; sincere; reliable. [1300–50; ME, var. of *livel* < MF < VL **libellum,* for L *libella* plummet line, level, dim. of *libra* balance, scales (see CASTLE)] —**lev′el•ly,** *adv.* —**lev′el•ness,** *n.*

lev′el cross′ing, *n. Brit.* GRADE CROSSING. [1835–45]

lev•el•er (lev′ə lər), *n.* 1. a person or thing that levels. 2. a person or thing that promotes the abolition of inequalities or other distinctions between people. Also, *esp. Brit.,* **leveller.** [1590–1600]

lev•el•head•ed (lev′əl hed′id), *adj.* having common sense and sound judgment; sensible. [1875–80, *Amer.*] —**lev′el•head′ed•ly,** *adv.* —**lev′el•head′ed•ness,** *n.*

lev′eling rod′, *n.* ROD (def. 15). [1900–05]

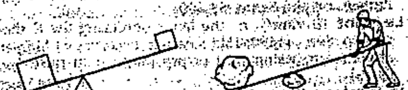
lev•el•ler (lev′ə lər), *n.* 1. *Chiefly Brit.* LEVELER. 2. (*cap.*) a member of a radical group organized during the English Civil War, advocating political equality and religious tolerance. [1590–1600]

lev′el play′ing field′, *n.* a state of equality; an equal opportunity. [1980–85]

Le•ven (lē′vən), *n.* **Loch,** a lake in E Scotland: ruins of a castle in which Mary Queen of Scots was imprisoned.

lev•er (lev′ər, lē′vər), *n.* 1. a rigid bar that pivots about one point and that is used to move an object at a second point by a force applied at a third. 2. a means or agency of persuading or of achieving an end. —*v.t.* 3. to move or lift with or as if with a lever. —*v.i.* 4. to use a lever. [1250–1300; ME *levere, levour* for **lever* < AF; OF *levier* = *lev(er)* to lift (< L *levāre* to lighten, lift) + *-ier* -IER[2]]

levers (def. 1)



lev•er•age (lev′ər ij, lev′rij; lē′vər ij, -vrij), *n., v.,* **-aged, -ag•ing.** —*n.* 1. the action of a lever. 2. the mechanical advantage or power gained by using a lever. 3. power or ability to act effectively or to influence people. 4. the use of a small initial investment to gain a relatively high return. —*v.t.* 5. to exert power or influence on. 6. to provide with leverage. 7. to speculate in (invested funds) by using leverage. [1715–25]

lev′eraged buy′out, *n.* the purchase of a company with borrowed money, using the company's assets as collateral, and often discharging the debt and realizing a profit by liquidating the company. *Abbr.:* LBO

lev•er•et (lev′ər it), *n.* a young hare. [1400–50; late ME < AF, dim. of *levre,* OF *lievre* < L *leporem,* acc. of *lepus* hare; see -ET]

Le•ver•ku•sen (lā′vər ko͞o′zən), *n.* a city in North Rhine-Westphalia, in W Germany, on the Rhine. 161,832.

Lev•er•tov (lev′ər tôf′, -tof′), *n.* **Denise,** 1923–97, U.S. poet, born in England.

Le•vi (lē′vī, lā′vē), *n.* 1. a son of Jacob and Leah. Gen. 29:34. 2. one of the 12 tribes of Israel, traditionally descended from him. 3. original name of MATTHEW (def. 1). 4. a Levite.

lev•i•a•ble (lev′ē ə bəl), *adj.* 1. capable of being levied. 2. liable or subject to a levy. [1475–85]

le•vi•a•than (li vī′ə thən), *n.* 1. (*often cap.*) (in the Bible) a sea monster. 2. any huge marine animal, as the whale. 3. something of immense size or power. [1350–1400; ME < LL < Heb *liwyāthān*]

lev•i•er (lev′ē ər), *n.* a person who levies. [1485–95]

lev•i•gate (lev′i gāt′), *v.t.,* **-gat•ed, -gat•ing.** to rub, grind, or reduce to a fine powder, with or without the addition of a liquid. [1605–15; < L *lēvigātus,* ptp. of *lēvigāre* to smooth, pulverize = *lēv(is)* smooth + *-igāre* v. suffix (cf. FUMIGATE)] —**lev′i•ga′tion,** *n.*

Le•vi-Mon•tal•ci•ni (lev′ē mon′tal chē′nē, lā′vē-), *n.* **Rita,** born 1909, Italian neurophysiologist: Nobel prize for physiology or medicine 1986.

lev•i•rate (lev′ər it, -ə rāt′, lē′vər it, -və rāt′), *n. Judaism.* the custom of marriage between a man and his brother's widow, required in Biblical law under certain circumstances. Deut. 25:5–10. [1715–25; < L *lēvir* husband's brother (akin to OE *tācor,* Gk *daēr,* Skt *devar*) + -ATE[1]] —**lev•i•rat•ic** (lev′ə rat′ik, lē′və-), **lev′i•rat′i•cal,** *adj.*

Le•vi's (lē′vīz), (*used with a pl. v.*) *Trademark.* a brand of jeans, esp. blue jeans.

Lé•vi-Strauss (lā′vē strous′), *n.* **Claude,** born 1908, French anthropologist, born in Belgium: founder of structural anthropology.

lev•i•tate (lev′i tāt′), *v.,* **-tat•ed, -tat•ing.** —*v.i.* 1. to rise or float in the air, esp. as a result of a supernatural power. —*v.t.* 2. to cause to rise or float in the air. [1665–75; LEVIT(Y) + -ATE[1], on the model of *gravitate*] —**lev′i•ta′tion,** *n.* —**lev′i•ta′tor,** *n.* —**lev′i•ta′tion•al,** *adj.*

Le•vite (lē′vīt), *n.* 1. a member of the tribe of Levi, esp. one appointed to assist the Temple priests. 2. a descendant of the tribe of Levi, having honorific religious duties. [1250–1300; ME < LL *Lēvīta* < Gk *Leuítēs* Levite, < *Leuí* (< Heb *Lēwī* Levi, Levite)]

Le•vit•i•cal (li vit′i kəl), *adj.* 1. of or pertaining to the Levites. 2. of or pertaining to Leviticus or the law (**Levit′ical law′**) contained in Leviticus. [1525–35] —**Le•vit′i•cal•ly,** *adv.*

Le•vit•i•cus (li vit′i kəs), *n.* the third book of the Bible, containing laws chiefly concerning the priests and Jewish ceremonial observance. [< LL *Lēviticus (liber)* Levitical (book) < Gk *Leuitikós.* See LEVITE, -IC]

Lev•it•town (lev′it toun′), *n.* a town on W Long Island, in SE New York. 57,045.

lev•i•ty (lev′i tē), *n., pl.* **-ties.** 1. lightness of mind, character, or behavior, esp. when inappropriate. 2. an instance or exhibition of this. 3. fickleness. [1555–65; < L *levitās* < *levis* light]

Lev•kas (lef käs′), *n.* an island in the Ionian group, off the W coast of Greece. 114 sq. mi. (295 sq. km).

levo-, a combining form meaning "left": *levorotatory; levoglucose.* [repr. L *laevus* left, on the left; see -O-]

le•vo•do•pa (lē′və dō′pə), *n.* L-DOPA. [1965–70]

le•vo•ro•ta•to•ry (lē′və rō′tə tôr′ē, -tōr′ē) also **le•vo•ro•ta•ry** (-rō′tə rē), *adj.* turning to the left, esp. rotating to the left of the plane of polarization of light: *levorotatory crystals. Symbol:* l [1870–75]

lev•y (lev′ē), *n., pl.* **lev•ies,** *v.,* **lev•ied, lev•y•ing.** —*n.* 1. an imposing or collecting, as of a tax, by authority or force. 2. the amount owed or collected. 3. the conscription of troops. 4. the troops conscripted. —*v.t.* 5. to impose (a tax, fine, etc.): *to levy a duty on imports.* 6. to conscript (troops). 7. to start or wage (war). —*v.i.* 8. to seize or attach property by judicial order. [1375–1425; late ME *leve(e)* < MF, use of fem. ptp. of *lever* to raise; see LEVER]

lewd (lo͞od), *adj.* **-er, -est.** 1. inclined to, characterized by, or inciting to lust or lechery; lascivious. 2. obscene or indecent, as language. 3. *Obs.* [bef. 900; ME *leud, lewed,* OE *lǣwede* lay, unlearned] —**lewd′ly,** *adv.* —**lewd′ness,** *n.*

Lew•es (lo͞o′is), *n.* a city in East Sussex, in SE England: battle 1264. 84,400.

lew•is (lo͞o′is), *n.* a device for lifting a dressed stone, consisting of a number of pieces fitting together to fill a dovetailed recess cut into the stone. [1730–40; perh. after the surname of the inventor]

Lew•is (lo͞o′is), *n.* 1. **C(ecil) Day,** DAY-LEWIS, Cecil. 2. **C(live) S(taples)** ("Clive Hamilton"), 1898–1963, English novelist and essayist. 3. **Edward,** born 1918, U.S. physician: Nobel prize 1995. 4. **(Harry) Sinclair,** 1885–1951, U.S. writer: Nobel prize 1930. 5. **John L(lewellyn),** 1880–1969, U.S. labor leader. 6. **Meriwether,** 1774–1809, U.S. explorer: leader of the Lewis and Clark expedition 1804–06. 7. **(Percy) Wyndham,** 1884–1957, English writer and painter, born in the U.S.

Lew•i•sham (lo͞o′ə shəm), *n.* a borough of Greater London, England. 231,600.

lew•is•ite (lo͞o′ə sīt′), *n.* a pale yellow, odorless compound, $C_2H_2AsCl_3$, used as a vesicant in World War I. [1920–25; after Winford Lee *Lewis* (1878–1943), U.S. chemist who developed it; see -ITE]

Lew′is with Har′ris, *n.* the northernmost island of the Outer Hebrides, in NW Scotland. 825 sq. mi. (2135 sq. km). Also called **Lewis and Har′ris.**

lex (leks), *n., pl.* **le•ges** (lē′jēz; *Lat.* le′ges). LAW[1]. [1490–1500]

lex., 1. lexical. 2. lexicon.

lex•eme (lek′sēm), *n.* a minimal lexical unit in a language, as a word or idiomatic phrase, esp. an abstract form underlying any inflected forms. [1935–40; LEX(ICAL) or LEX(ICON) + -EME]

lex•i•cal (lek′si kəl), *adj.* 1. of or pertaining to the words or vocabulary of a language, esp. as distinguished from its grammatical and syntactic aspects. 2. of, pertaining to, or of the nature of a lexicon. [1830–40] —**lex′i•cal′i•ty,** *n.* —**lex′i•cal•ly,** *adv.*

lex′ical mean′ing, *n.* the meaning of a base morpheme or word, independent of its use within a construction. Compare GRAMMATICAL MEANING. [1930–35]

lexicog., 1. lexicographer. 2. lexicographic. 3. lexicography.

lex•i•cog•ra•pher (lek′si kog′rə fər), *n.* a writer, editor, or compiler of a dictionary. [1650–60; < LGk *lexikográphos.* See LEXICON, -GRAPHER]

lex•i•cog•ra•phy (lek′si kog′rə fē), *n.* 1. the writing, editing, or compiling of dictionaries. 2. the principles and procedures involved in writing, editing, or compiling dictionaries. [1670–80] —**lex′i•co•graph′ic** (-kə graf′ik), **lex′i•co•graph′i•cal,** *adj.* —**lex′i•co•graph′i•cal•ly,** *adv.*

lex•i•col•o•gy (lek′si kol′ə jē), *n.* the study of the formation, meaning, and use of words. [1820–30] —**lex′i•co•log′i•cal** (-kə loj′i kəl), **lex′i•co•log′ic,** *adj.* —**lex′i•col′o•gist,** *n.*

lex•i•con (lek′si kon′, -kən), *n., pl.* **-ca** (-kə), **-cons.** 1. a wordbook or dictionary, esp. of Greek, Latin, or Hebrew. 2. the vocabulary of a particular language, field, social class, person, etc. 3. the total inventory of words or morphemes in a given language. [1595–1605; < ML < MGk, Gk *lexikón,* n. use of neut. of *lexikós* of words]

lex•i•co•sta•tis•tics (lek′si kō stə tis′tiks), *n.* (*used with a sing. v.*) the statistical study of the vocabulary of a language or languages for historical purposes. [1955–60]

Lex•ing•ton (lek′sing tən), *n.* 1. a town in E Massachusetts, near Boston: first battle of the American Revolution fought here April 19, 1775. 29,479. 2. a city in N Kentucky. 239,942.

lex•is (lek′sis), *n.* the vocabulary of a language, esp. as distinguished

lev•el (lev′əl), *adj., n., v.,* **-eled, -el•ing** or (*esp. Brit.*) **-elled, -el•ling.** —*adj.* **1.** having no part higher than another; having a flat or even surface. **2.** being in a plane parallel to the plane of the horizon; horizontal. **3.** equal, as in height, condition, status, or advancement. **4.** even, equable, or uniform: *to speak in a level voice.* **5.** filled to a height even with the rim of a container: *a level teaspoon of salt.* **6.** mentally well-balanced; sensible; rational: *to keep a level head in a crisis.* **7.** of or pertaining to a particular rank or involving members of such a rank (usu. used in combination): *high-level discussions.* —*n.* **8.** the horizontal line or plane in which anything is situated, with regard to its elevation: *a shelf built at eye level.* **9.** a position with respect to a given or specified height: *The water rose to a level of 30 feet.* **10.** a position or plane in a graded scale of values: *an average level of skill.* **11.** rank or status, as in a hierarchy: *the top levels of government.* **12.** stratum or sphere: *levels of meaning; elections on a local level.* **13.** an extent, measure, or degree of intensity, concentration, quantity, etc.: *low levels of radiation; to increase levels of production.* **14.** a horizontal surface, as a floor in a building or other structure: *the upper level of the bridge.* **15.** a device, as a spirit level, used for determining or adjusting something to a horizontal surface. **16. a.** a surveying instrument consisting of a spirit level mounted on a frame with a telescopic sight, used for establishing a horizontal. **b.** an observation made with this instrument. **17.** an imaginary line or surface everywhere at right angles to the plumb line. **18.** a horizontal position or condition. **19.** a level or flat surface, as an extent of land approximately horizontal and

unbroken by irregularities. **20.** the interconnected horizontal mine workings at a particular elevation or depth: *the 1500-foot level.* —*v.t.* **21.** to make (a surface) level, even, or flat; make horizontal. **22.** to raise or lower to a particular level or position. **23.** to bring (something) to the level of the ground: *to level trees.* **24.** *Informal.* to knock down (a person). **25.** to make equal, as in status or condition. **26.** to make even or uniform, as coloring. **27.** to aim or point (a weapon, criticism, etc.) at a mark or objective. **28.** to find the relative elevation of different points in (land), as with a surveyor's level. —*v.i.* **29.** to bring things or persons to a common level. **30.** to aim a weapon, criticism, etc., at a mark or objective. **31.** to speak truthfully and openly (often fol. by *with*). **32. a.** to take a level in surveying. **b.** to use a leveling instrument. **33. level off, a.** (of an aircraft) to maintain a constant altitude after a climb or descent. **b.** to become stable; reach a constant or limit. **c.** to make even or smooth. —***Idiom.*** **34. find one's (own) level,** to attain a position or status that matches one's ability. **35. one's level best,** one's very best; one's utmost. **36. on the level,** honest; sincere; reliable. [1300–50; ME, var. of *livel* < MF < VL **lībellum*, for L *lībella* plummet line, level, dim. of *lībra* balance, scales (see CASTLE)] —**lev′el•ly,** *adv.* —**lev′el•ness,** *n.*